工學博士 學位論文

Concise total Synthesis of Tropoloisoquinolines and Process Development of Bio-based Adipic Acid from Galactose

트로폴로아이소퀴놀린화합물의 간결화한 전합성 및 갈락토오스 유래 바이오 기반 아디픽산 합성공정 개발

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申나라

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Concise Total Synthesis of Tropoloisoquinolines and Process Development of Bio-based Adipic Acid from Galactose

by

Nara Shin

Submitted in partial fulfillment of the Requirements for

The Degree of Doctor of Philosophy

at The Graduate School of Seoul National University

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Thesis Adviser: Young Gyu Kim

Abstract

Concise Total Synthesis of Tropoloisoquinolines and Process Development of Bio-based Adipic Acid from Galactose

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This thesis comprises two chapters. Chapter 1 describes the concise total synthesis of tropoloisoquinolines via radical anionic coupling. Chapter 2 describes the process development of bio-based adipic acid from galactose by utilizing deoxydehydration process to remove oxygen contents.

Chapter 1. Tropoloisoquinoline alkaloids isolated from a plant family, Menispermaceae, which exhibit significant cytotoxic activity against leukemia P388 cell line. Motivated by its high cytotoxicity and unique structure, more concise and divergent syntheses of tropoloisoquinolines were accomplished by using commercially available bromoisoquinolines, based on previously established synthetic strategy employing radical anionic coupling of phenolic nitronate. The key intermediate, phenolic nitronate, was prepared by palladium-catalyzed coupling reaction between phenols and isoquinolines and following Reissert-type nitromethylgroup addition. As a result, various tropoloisoquinoline alkaloids including pareitropone have been synthesized

and these compounds should be useful for structure-activity relationship (SAR) study. In the analogs, the number of the methoxy groups has been controlled from 0 to 3 and tropone moiety modified to chlorinated tropone. In particular, chlorinated tropone could be used for further functionalization on the tropone moiety.

Chapter 2. Adipic acid, one of the commercially important dicarboxylic acids, was efficiently prepared from galactaric acid via deoxydehydration (DODH) process. DODH reaction was applied to remove two pairs of vicinal diols in galactaric acid, with the use of oxo-rhenium catalyst affording corresponding a key intermediate, muconate, First, an efficient large scale one-pot process was established for the mass production on bio-based adipic acid. The desired bio-based adipic acid was achieved in one-pot process that is consists of 4-step reaction: 1) esterification, 2) rhenium-catalyzed DODH reaction, 3) palladium-catalyzed hydrogenation, 4) hydrolysis. With our facile and green synthetic one-pot process, adipic acid was obtained at overall yield of 64% in high purity in 18 g scale from galactaric acid. Second, recyclable green process for bio-based adipic acid was developed by using ionic liquid as a reaction media. Relatively rare and expensive rhenium catalyst was recycled dissolved in ionic liquid. With ionic liquid-mediated DODH reaction, bio-based adipic acid was synthesized in quantitative yield, and the recovered ionic liquid was reused more than 10 times, affording the desired key intermediate muconate with similar yields.

Keywords: tropoloisoquinoline alkaloids, radical anionic coupling, anti-leukemic activity, bio-based adipic acid, deoxydehydration (DODH), rhenium, ionic liquid-mediated reaction,

Student Number: 2010-20996

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List of Abbreviations

Abbr.	Abbreviations
AcOH	Acetic acid
[C_2MIm]	1-Ethyl-3-metylimidazolium
[C_4MIm]	1-Butyl-3-metylimidazolium
[C_4MPyrr]	1-Butyl-1-methylpyrrolidinium
[C_6MIm]	1-Hexyl-3-metylimidazolium
[C_6MPyrr]	1-Hexyl-1-methylpyrrolidinium
[C_8MIm]	3-Methyl-1-octylimidazolium
[C_8MPyrr]	1-Methyl-1-hexyylpyrrolidinium
CCD	Charge-coupled device
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	4,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile
DMSO	Dimethylsulfoxide
DODH	Deoxydehydration
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
ICP-Ms	Inductively coupled plasma - mass spectroscopy
IL	Ionic liquid
LD_{50}	Lethal dose, 50%
LHMDS	Lithium hexamethyldisilazide
Mesy	Methanesulfonate
MTO	Methyltrioxorhenium
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
OAc	Acetate
SAR	Structure-activity relationship

TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
TfO(or OTf)	Trifluoroacetate
TFSI	Bis(trifluoromethanesulfonyl)imide
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Tetramethylsilane, Trimethylsilyl
***p*-TsOH**	*p*-Toluenesulfonic acid

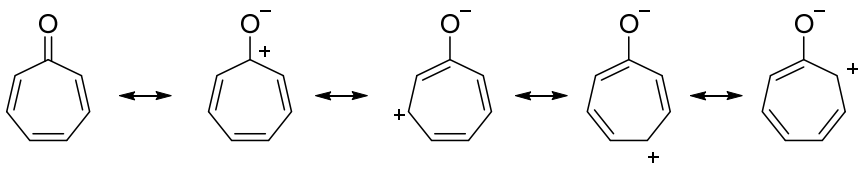
Chapter I

Concise total synthesis of tropoloisoquinolines

Introduction

1. Tropoloisoquinoline alkaloids

Tropoloisoquinolines are naturally occurring alkaloids having unique structure of annulated tropone and isoquinoline. Tropone is a kind of heptafulvene analog, cyclic polyenes with unsaturated exocyclic substituents, and known to own aromaticity due to the contribution of resonance form which is similar with tropylium ion (Scheme 1).[1] The annulated ring structure consisting of two aromatic rings made tropoloisoquinolins flat, which was revealed by x-ray crystalography.[2]



Scheme 1. Resonance structure of tropone

This family is composed of following six compounds up to now: Pareitropone (**1c**), pareirubrine, grandirubrine, pareirubrine A, isoimerubrine,

imerubrine (Fiqure 1). These tropoloisoquinolines were isolated from a plant family, Menispermaceae (*Abuta refescens, Abuta concolor,* and *Cissampelos pareira*).[2] It was elucidated for not only predominant anti-leukemic activity against P388 or L1210[2f-j] but also cytotoxic activity against several human cancer cell lines (HCT-116 colon adenocarcinoma, ACHN renal carcinoma, and A549 lung carcinoma).[2k] Imerubrine was isolated at first in 1975,[2c-d] and then grandirubrine and isoimeruburine were isolated 1980 respectively.[2e]

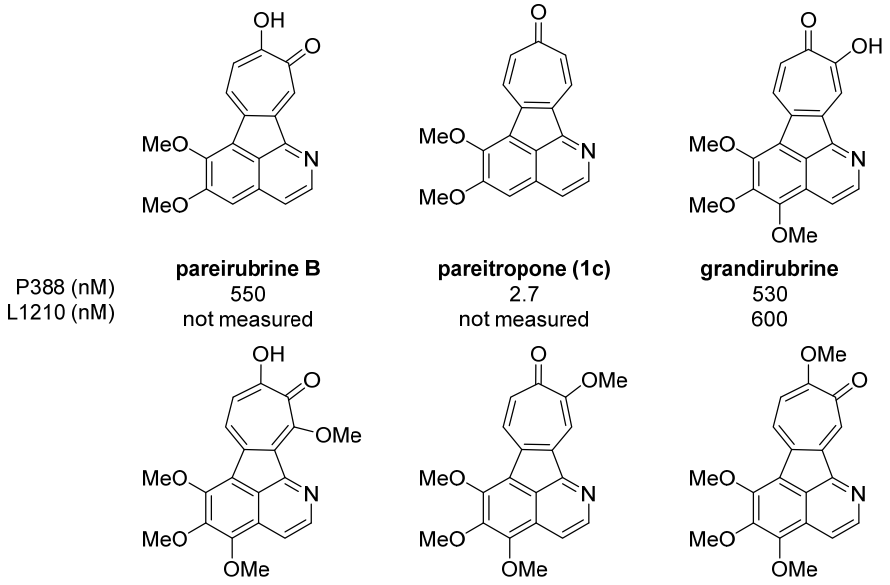


Figure 1. Tropoloisoquinolins and its anti-leukemic activity[3b]

Pareitropone, pareirubrin A and B have also been found by H. Itokawa's group during the research for novel anti-leukemic extracts from South American medical plants, *Cissampelos pareira*.[2f-1] Among those isoquinoline alkaloids, pareitropone shows vastly superior anti-leukemic activity (IC_{50} = 2.7 nM against the leukemia P388 cell line).[2i] Although mechanism of anti-leukemic activity of tropoloisoquinolines have not been demonstrated up to date, it is hypothesized that its planar structure annulated two aromatic ring attribute anti-leukemic activity by the mechanism involving DNA intercalation based on the action of protoberberine and aporphinoid, another members of isoquinoline alkaloids.[4] According to another study on common receptor complement feature among some anti-leukemic compounds, it appeared that the triangular pattern may also contribute in the binding to one of the pertinent receptor site in biopolymers involved in leukemia geneses (Figure 2).[5]

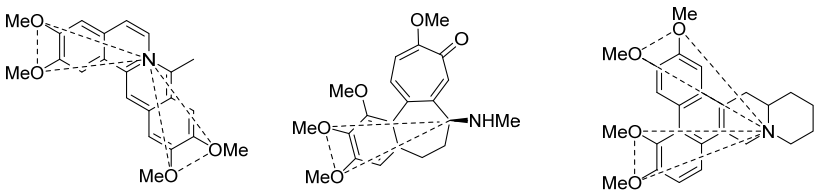


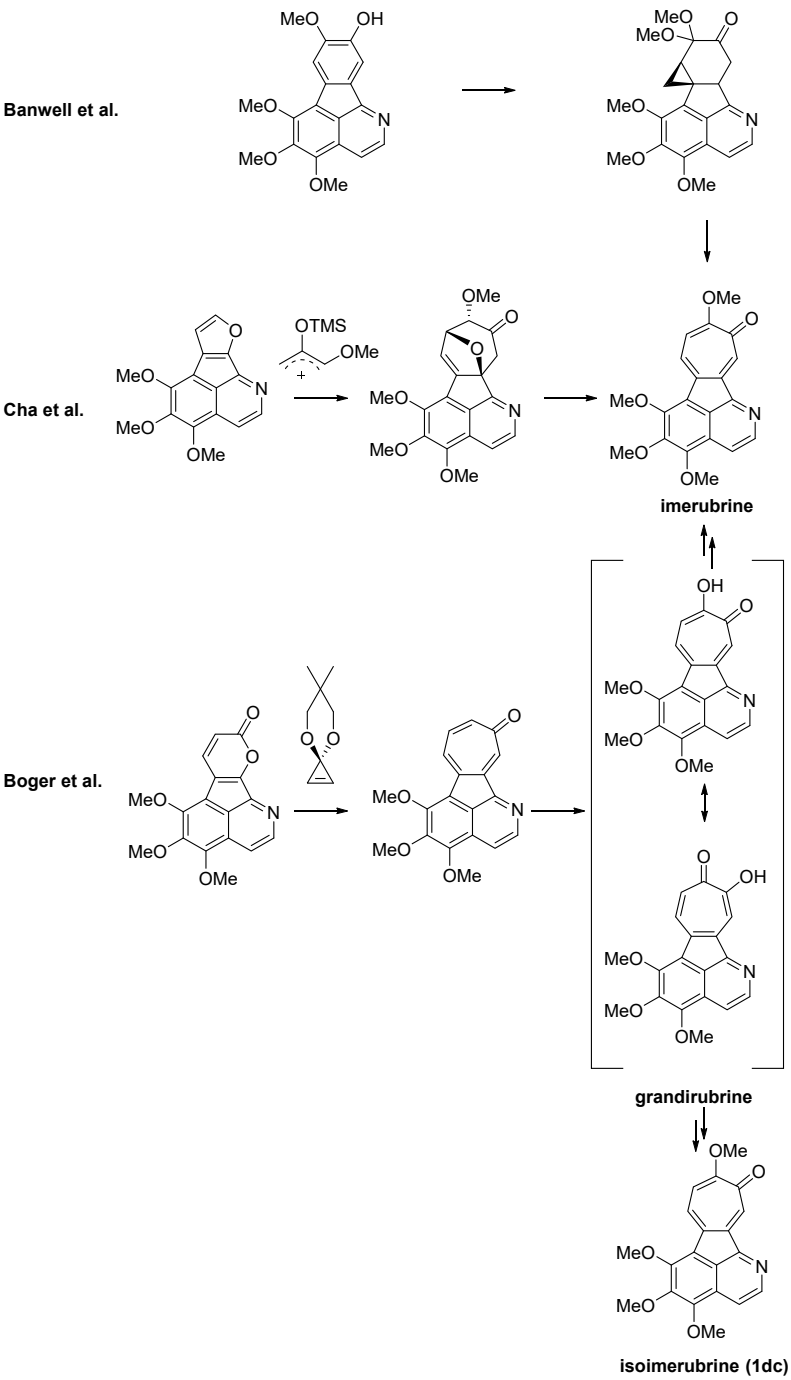
Figure 2. Common N-O-O triangular pattern among some anti-leukemic compounds

The potent cytotoxicity and unique structure of tropoloisoquinolines provoked interest to develop more concise and divergent synthetic methodology, therefore, I wish to herein describe the total synthesis of various tropoloisoquinolines including naturally occurring pareitropone and isoimerubrine.[3]

2. Previous synthetic studies toward tropoloisoquinolin alkaloids

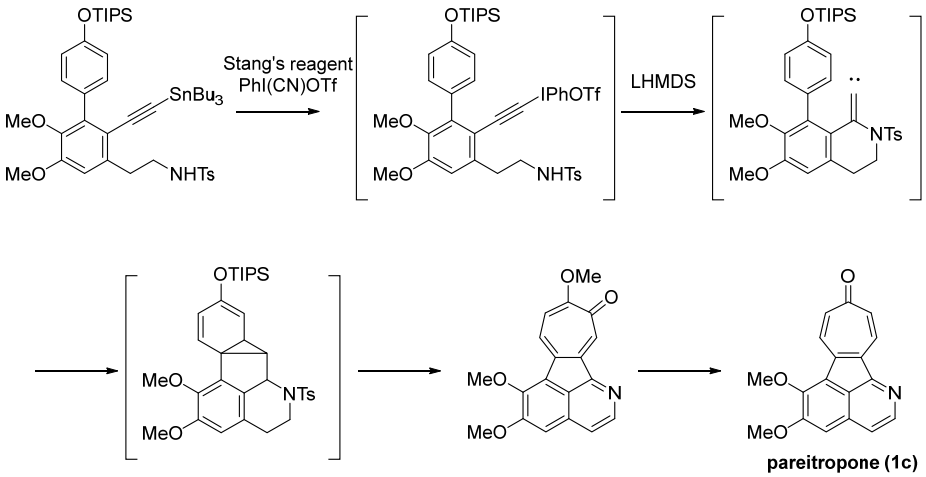
Due to its unique structure and potent cytotoxicity, total synthesis of tropoloisoquinolines have been attracted many attentions in organic chemistry. As a result, total synthesis of imeruburine, the first total synthesis of a tropoloisoquinoline alkaloid, was successfully accomplished by Banwell *et al*. in 1994.[6a] They constructed upper side tropone ring, the key intermediate, from ring-fused σ-homo-o-benzoquinone mono acetal by treatment with TFA.

Then, in next year, Boger *et al*. was synthesized grandirubrine along with imerburine and isoimerubrine which are prepared by methylation of grandiruburine existing a tautomeric mixture.[2j] Based on the [4+2] cycloaddition reaction and subsequent retro-Diels-Alder reaction with loss of CO_2, the desired tropone moiety was formed. Cha *et al*. also reported the total synthesis of tropoloisoquinolines of imerubrine, isoimerubrine and grandirubrine.[6b] The [4 + 3] cycloaddition reaction of an oxy allyl to a suitably functionalized furan, followed by double elimination of the resulting oxa bridge, provided ready access to the tropoloisoquinoline alkaloids, imerubrine, grandirubrine, and isoimerubrine (Scheme 2).



Scheme 2. Previous synthetic study toward Tropoloisoquinolines [3b]

Following various total synthesis of tropoloisoquinolines, recently, the first total synthesis of pareitropone have been reported by Feldman *et al.*[7] Different from previously applied ring formation methods, they directly constructed 10-ketotropone ring of pareitropone by alkynyliodonium salt chemistry. Stang's reagent (PhI(CN)OTf) was used to introduce alkynyliodonium salt which was converted to heptatriene through alkynylidene carbine intermediate by the action of LHMDS. By addition of KF on Al_2O_3, pareitropone was prepared in 7% yield over 14 steps (Scheme 3).



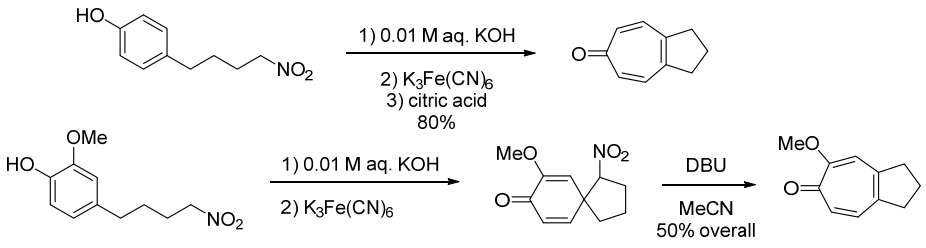
Scheme 3. Total synthesis of pareitropone by Feldman *et al.*

3. Radical anionic coupling

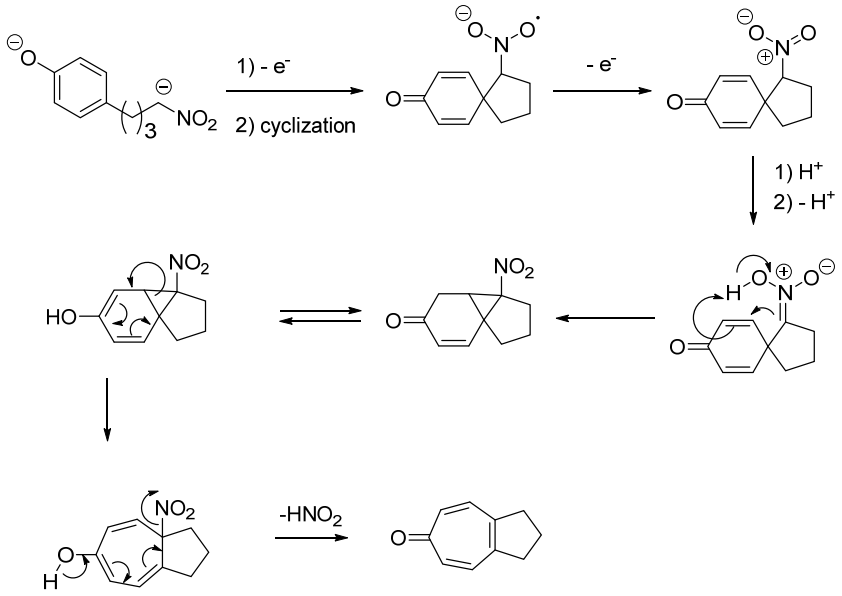
In order to efficiently construct the key structure of tropone moiety, we employed a radical anionic coupling reaction of phenolic nitronate. This concept of reaction, phenol nitrate coupling, was firstly reported by Kende *et al.* in 1986 (Scheme 4).[8]

Under the strong basic condition of potassium hydroxide, the dianion was formed and then it was simultaneously transformed to spirocyclic nitropentane with radical initiator of $K_3Fe(CN)_6$ via oxidative intramolecular radical coupling. The following rearrangement of obtained spirocycle furnished tropone or tropolone in the presence of DBU or citric acid.

Since the basic condition for generation of dianion is crucial for the overall ring formation, the excess amount of base is required for the efficient reaction even though only 2 equivalents of base is needed on the basis of mechanism (Scheme 5).



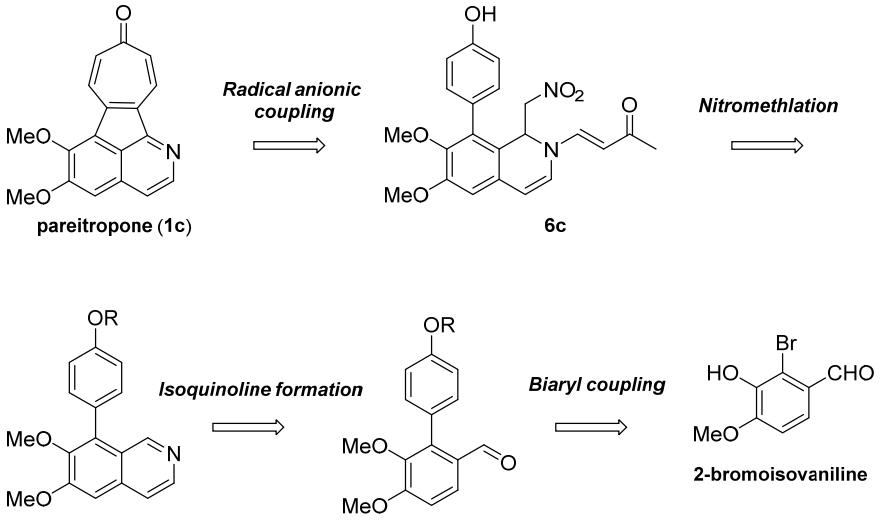
Scheme 4. Phenol nitrate coupling by Kende *et al.*



Scheme 5. Proposed mechanism of kende coupling

4. Previous total synthesis of pareitropone via radical anionic coupling

Our group have recently reported total synthesis of pareitropone via radical anionic coupling, above explained, and its retrosynthetic analysis is described in scheme 6.



Scheme 6. Previous total synthesis of pareitropone

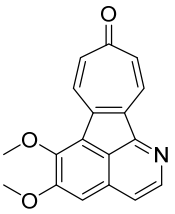
For the synthesis of pareitropone, a radical anionic coupling precursor, phenolic nitronate, was prepared via Reissert-type nitro methyl group addition. The isoquinoline was formed by Pomeranz-Frisch reaction from tosyl amide which was synthesized by palladium mediated coupling reaction between phenol and bromobezaldehyde. The bromobenzaldehyde was

prepared from commercially available 2-bromoisovaniline. Consequently, total synthesis of pareitropone has been achieved in 30% yield over 9 steps.[3a]

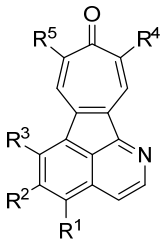
Result and Discussion

1. Concise reaction strategy for tropoloisoquinoline

The success of the pareitropone synthesis encouraged to develop more concise and divergent synthetic route for various tropoloisoquinolines including pareitropone (Fiqure 3). The original synthetic scheme proved the radical anionic coupling reaction to be efficient for the construction of the annulated tropone and isoquinoline moiety, however, isoquinoline formation was highly dependent on the substrate. Therefore, each reaction condition had to be specifically optimized for each substrate resulted in the lack of generality of the strategy.



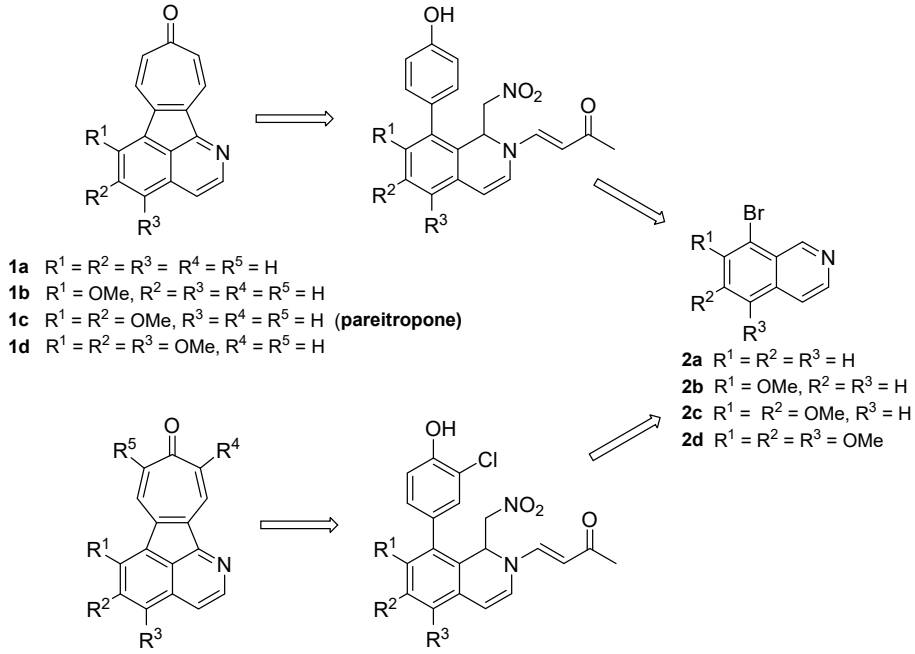
1c. Pareitropone



1a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
1b $R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H$
1d $R^1 = R^2 = R^3 = OMe, R^4 = R^5 = H$
1ca $R^1 = R^2 = OMe, R^3 = H, R^4 = Cl, R^5 = H$
1cb $R^1 = R^2 = OMe, R^3 = H, R^4 = H, R^5 = Cl$
1da $R^1 = R^2 = R^3 = OMe. R^4 = Cl, R^5 = H$
1db $R^1 = R^2 = R^3 = OMe, R^4 = H, R^5 = Cl$
1dc $R^1 = R^2 = R^3 = OMe. R^4 = OMe, R^5 = H$ (**isoimerubrine**)
1dd $R^1 = R^2 = R^3 = OMe, R^4 = H, R^5 = OMe$

Figure 3. Structure of Pareitropone and its analogs

To overcome this limitation, we have approached in convergent manner to develop more efficient and concise synthetic strategy starting from commercially available bromoisoquinolines (Scheme 7). The change of starting materials make it possible to easily synthesize pareitropone and its analogs, regardless of substrate with a common synthetic scheme at the stage of isoquinoline ring formation. Furthermore, the modified scheme consists of 5~7 steps which is much fewer than the original scheme of more than 9 steps.



1a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
1b $R^1 = OMe$, $R^2 = R^3 = R^4 = R^5 = H$
1c $R^1 = R^2 = OMe$, $R^3 = R^4 = R^5 = H$ (**pareitropone**)
1d $R^1 = R^2 = R^3 = OMe$, $R^4 = R^5 = H$

2a $R^1 = R^2 = R^3 = H$
2b $R^1 = OMe$, $R^2 = R^3 = H$
2c $R^1 = R^2 = OMe$, $R^3 = H$
2d $R^1 = R^2 = R^3 = OMe$

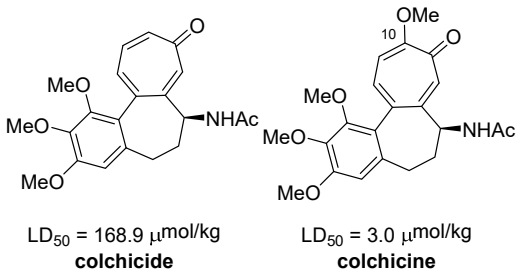
1ca $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = Cl$, $R^5 = H$
1cb $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = Cl$
1da $R^1 = R^2 = R^3 = OMe$. $R^4 = Cl$, $R^5 = H$
1db $R^1 = R^2 = R^3 = OMe$, $R^4 = H$, $R^5 = Cl$
1dc $R^1 = R^2 = R^3 = OMe$. $R^4 = OMe$, $R^5 = H$ **(isoimerubrine)**
1dd $R^1 = R^2 = R^3 = OMe$, $R^4 = H$, $R^5 = OMe$

Scheme 7. Retrosynthetic analysis

With our newly developed efficient synthetic strategy, pareitropone and its diverse analogs having different extent of alkoxy substituents on the isoquinoline or chlorine substituents on the tropone, have been successfully synthesized.

According to previous reports, high toxicity of tropoloisoquinoline is expected to be governed by the unique annulated tropone and isoquinoline moiety.[1] However, as there have been no intensive SAR study to demonstrate exactly which structure is origin of the high cytotoxicity, thus, preparation of various analogs is required as a starting point for the SAR study.

Fully conjugated and annulated pareitropone structure is considered to be flat, 2-dimensional, except the substituted methoxy groups.[2f] Therefore, several analogs having different methoxy group have been prepared to demonstrate the relationship between the cytotoxic activity and 3-dimensional structure of methoxy group by comparing those of activities.



LD_{50} = 168.9 μmol/kg
colchicide

LD_{50} = 3.0 μmol/kg
colchicine

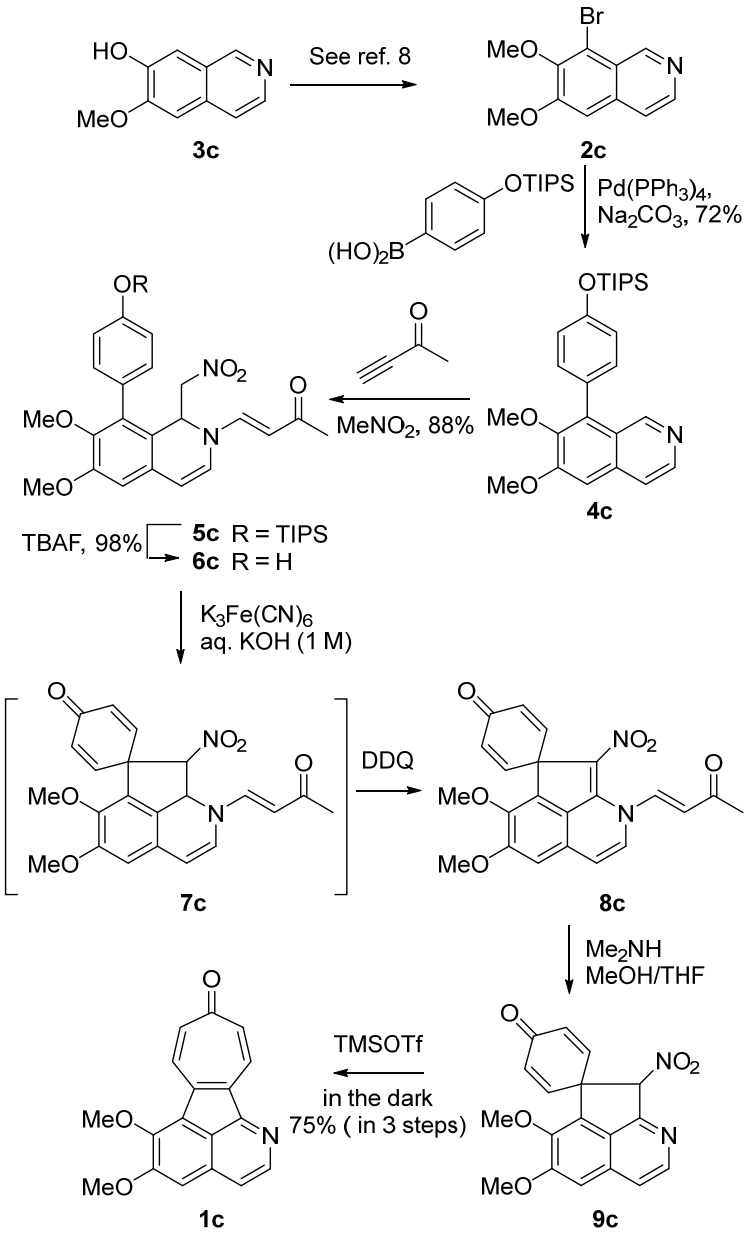
Figure 4. Cytotoxic activity of colchicine and colchicine

On the other hand, according to the previous result on colchicine, another member of tropoloisoquinoline, it is also could be anticipated that potent cytotoxicity was originated form tropone moiety (Figure 4).[9] Especially, the additional oxygen contents on C10 position was crucial for the biological activity. Thus, to clarify the relationship between biological activity and the nature of tropone moiety, the tropone moiety was further modified to the chlorinated tropone which have different electronic nature. The modified tropone is not only meaningful itself, but also have advantage that it can be readily converted into other functional groups. In reality, it was transformed into methoxy group, which proved usefulness of chlorinated tropone as an intermediate of another substituted tropone.

2. Concise total synthesis of pareitropone and its analogs

Pareitropone and its various analogs were prepared via newly developed synthetic strategy. These analogs also can be synthesized through previously developed linear synthetic scheme. However, reaction efficiency of isoquinoline formation was highly depends on the electronic properties of the upper side phenol and the number of methoxy groups present in the bottom side aryl component. To improve this inefficiency, a convergent strategy using commercially available isoquinolines have been applied. Thus the efficiency of installing a phenol moiety on isoquinoline is the most crucial throughout the overall synthesis.

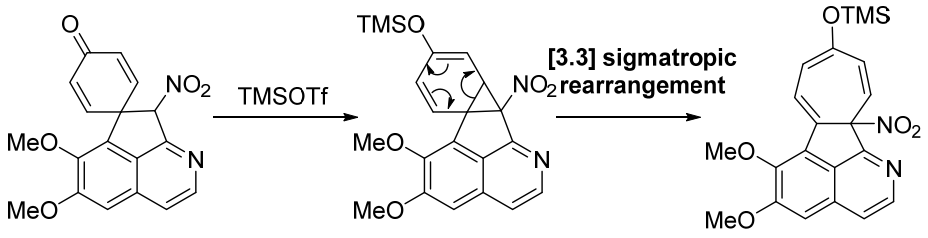
As described at scheme 7, the common retrosynthetic analysis started from the bromoisoquinolines **2**. The number of methoxy groups varies from 0 to 3, whereas the original pareitropone **1a** possesses two methoxy groups. The key reaction of radical anionic coupling of phenolic nitronate was successfully constructed the desired tropone moiety. The phenolic nitronate was prepared via Suzuki coupling followed by Reissert-type nitro methyl group introduction.



Scheme 8. Totally synthesis of pareitropone

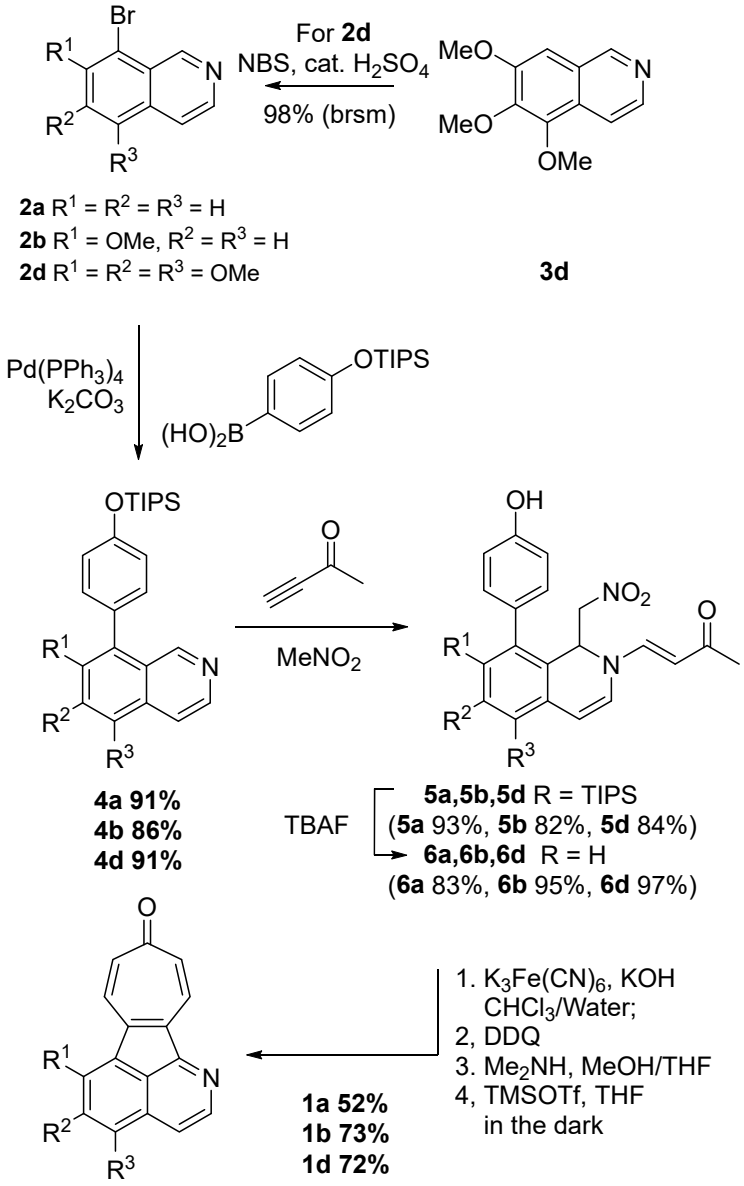
The research initiated from the synthesis of pareitropone (Scheme 8). The required bromoisoquinoline **2c** was synthesized from commercially available isoquinoline **3c** via the literature procedure.[10] The Suzuki coupling between the prepared phenolic boronic acid and bromoisoquinoline proceeded to afford the biaryl compound **4c** which was identical to the intermediate in the original scheme.[11,12] Fortunately, it was efficiently constructed with reduced steps but better yield. Then the nitromethyl group was added to the obtained compound **4c** affording compound **5c** with help of 3-butyn-2-one group according Yadav's procedure.[13] The free phenol **6c** ready for the radical anion coupling reaction was obtained after silyl group deprotection of **5c** by using TBAF. With action of radical initiator $K_3Fe(CN)_6$, the precursor **6c** was quickly converted to the corresponding spirocyclic intermediates **7c** under strong basic condition. However, the intermediate **7c** is extremely unstable to decompose even on the TLC resulting low efficiency of following rearrangement. On the other hand, the spiroolefine **8c,** which was obtained along with **7c,** was stable enough to be isolated and well converted to desired product. Therefore, the reaction was proceeded via **8c** which was obtained from **7c** as soon as formed by the action of DDQ. After simple extraction, to a solution of the obtained crude **8c** was added dimethyl amine in methanol solution to remove methyl vinyl ketone substituent on **8c** by forming acetal

intermediate. Interestingly, the elimination not occurred without methanol that might because methanolysis of resulting acetal is crucial for elimimation.[3e]



Scheme 9. Mechanistic consideration for the final rearrangement

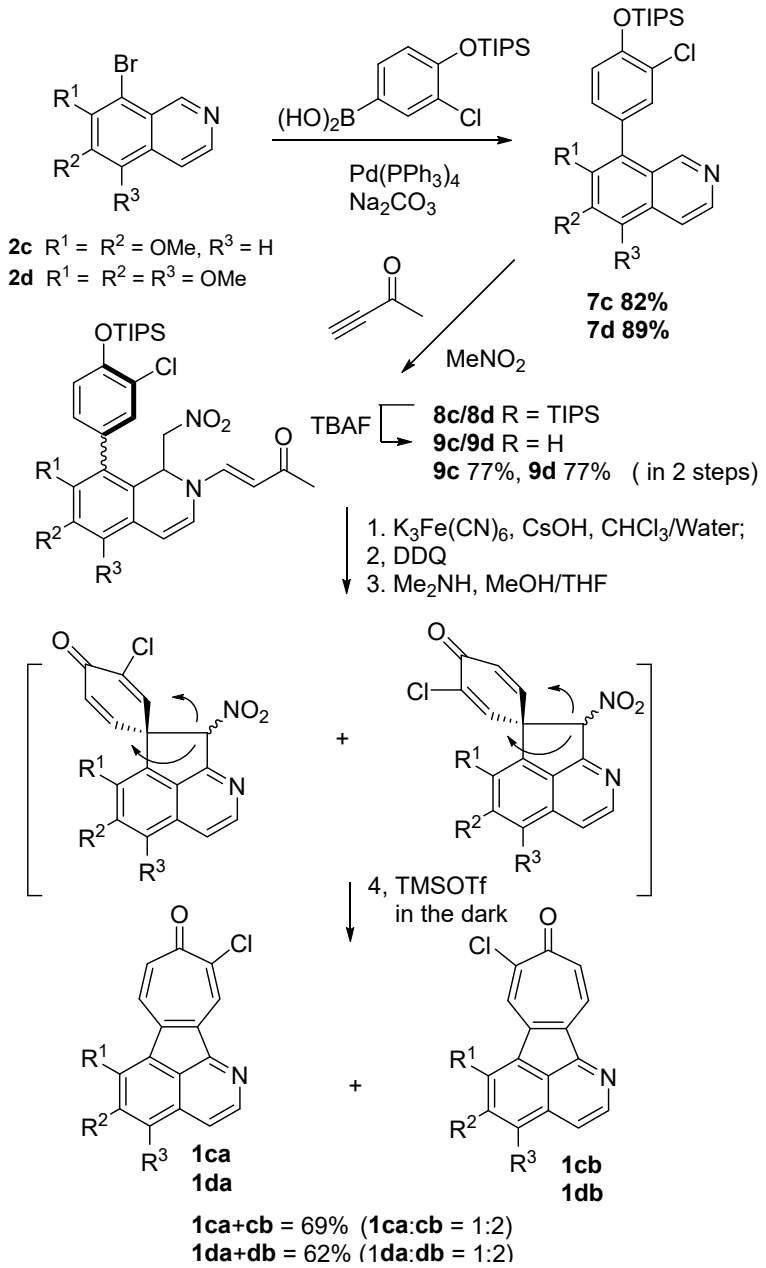
After evaporation of volatile residue, intermediate **9c** was treated with TMSOTf at 0 ºC in the dark for the rearrangement to the desired pareitropone **1c** in yield of 80% and the proposed mechanism is described in Scheme 9.



Scheme 10. Total synthesis for methoxy modified analogs

With the success of pareitropone synthesis, the research was extended to the preparation of its methoxy modified analogs (Scheme 10).

The reaction initiated with Suzuki coupling of phenol boronic acid and bromoisoquinolines **2a**, **2b, 2c**. The isoquinolines **2a-2b** were available through commercial suppliers. And the bromoisoquinoline **2d** was prepared from commercially available **3d** according to known procedure.[2f] Similar with pareitropone, the coupling reaction between obtained bromoisoquinolinese and phenolic boronic acid smoothly yielded the desired products **4a**, **4b**, and **4d** with good yield regardless of the number methoxy substituent. Then, with the help of 3-butyn-2-one**,** nitrometyl group was successfully introduced to the each isoquinolines of **4a**, **b, d,** following desilylation afforded the desired phonolic nitronates **6a, b, d**. The syntheses were completed under Kende's procedure with radical initiator $K_3Fe(CN)_6$. The desire products were synthesized through the same spirocyclic intermediates with pareitropon, which is spontaneously converted to the desired tropones by sequential treatment of methanolic diethyl amine and TMSOTf without further purification in one-pot. As a result, demethoxy analog **1a,** monomethoxy analog **1b,** and trimethoxy analogs **1d,** were successfully prepared with the yield of 52%, 73%, 72% respectively.



Scheme 11. Total synthesis for chlorinated tropone analogs

As a continuation of the study, we have carried out the synthesis of tropone modified analogs, chlorinated tropone (Scheme 11). At first, we attempted the syntheses with already functional group introduced phenol such as 2-methoxy phenol, 2-nitrophenol and 2-fluorophenol. But unfortunately all the reactions did not produce to the desired final products. In case of 2-nitro phenol, Suzuki coupling reaction did not successful. We assumed that is because the electron deficient 2-nitro phenol didn't converted to the corresponding boronic acid. On the other hand, 2-methoxy phenol and 2-fluorophenol were successfully converted to biary adducts which were also well converted to the radical anionic coupling precursor. However, the final rearrangement did not occdured, and it is the reason we chose the chlorophenol as a starting material. Luckily, chlorine functionality seemed to be appropriate for both of tropone construction and further functionalization. The synthesis was initiated by Suzuki coupling reaction between the bromoisoquinoline **2c-d** which already used once above, and 2-chlorophenyl boronic acid to afford corresponding biaryl adducts **7c-d**. Sometimes, desilylated product was obtained along with the desired product, which could be protected again with triisopropyl chloride under basic condition. Reissert-type addition of nitromethane followed by TIPS group deprotection was also well carried out to produce desired compounds **9c-d,**

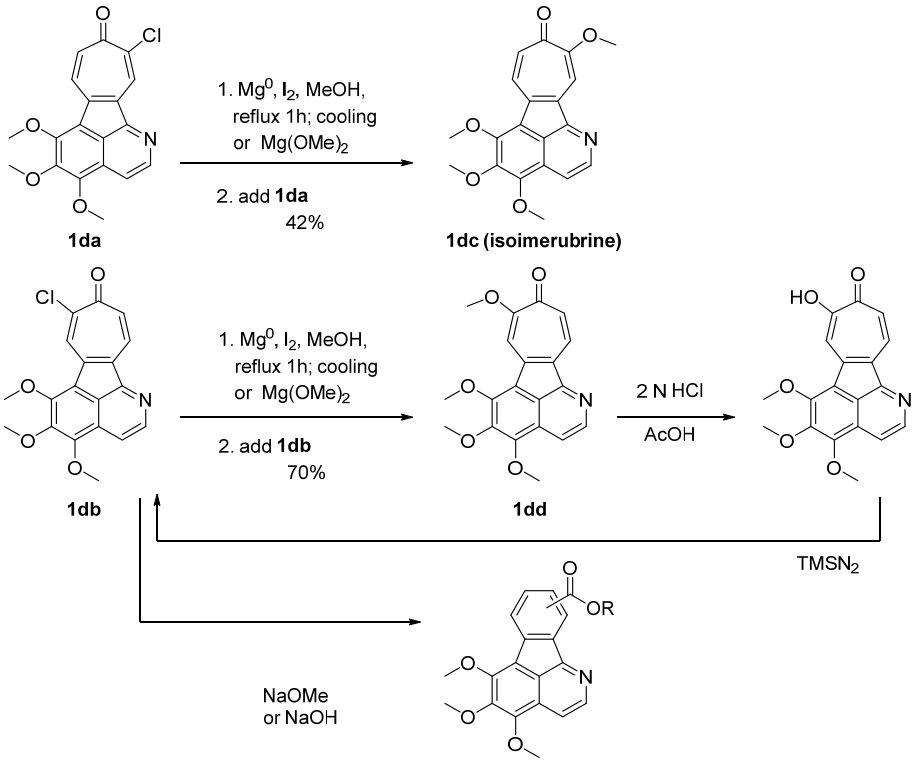
radical anionic precursor**.** However, the rigid biaryl precursor was obtained as a atropeisomeric mixture which derived from asymmetry of chlorophenol moiety. The isomeric mixture was exposed to radical anion coupling reaction and following butenone group elimination occurred to give the spirocyclic intermediate. Then the following treatment of TMSOTf finally furnished the chlorinated tropone analogs. Different from unsubstituted tropone, chlorinated derivatives treated under slightly modified reaction condition. In order to find better base than the originally used KOH, we considered various hydroxide, because hydroxide generally showed better result compared to alkoxide or amine base in our preliminary sturdy for pareitropone. As a result, $CsOH \cdot H_2O$ was selected as most appropriate hydroxide. After dianion was generated by base, radical anionic coupling occurred to furnish spirocyclic intermediates which were concurrently converted to the corresponding spiro-olefin compound by adding DDQ. Different from the case of unsubstituted phenol, the chlorinated spirocyclic intermediate was not completely converted to the spiro-olefin even in longer reaction time of 3 h which rather resulted in decreased yield. It is presumed that the relatively low reactive chlorinated spirocycle was interrupted by existing water when it reacted with DDQ. Therefore, in order to accelerate the reaction, existing water was remove by simple extraction, which was

proceeded quickly in the dark condition to prevent decomposition of spirocyclic intermediate. After another addition of 2 eq. of DDQ, the spirocyclic intermediate was fully transformed to spiro-olefin within 30 min.

After the butenone group elimination, for similar reason, the rearrangement of spiro-olefin was proceeded under hasher condition than the case of normal tropone. Temperature was elevated to room temperature from 0 ^{o}C and reaction time was prolonged to 1h for the full conversion, where, normal tropone was decomposed under that condition. Due to the asymmetry of upper side phenol derived from chlorine, the final product was also obtained as a regioisomeric mixture. In the case of dimethoxy isoquinoline, the yield was 69% in 1 to 2 ratio of **1ca** to **1cb** and the yield of trimethoxy isioquinoline was 62% in the ratio of 1 to 2 of **1da** to **1db.**

3. Structure determination of chlorinated tropoloisoquinolins

In order to determine the exact structure and testify the feasibility of further functionalization, obtained chlorinated tropone mixture were substituted with methoxy group. Interestingly, when compound **1db** was treated with sodium methoxide or sodium hydroxide, undesired product was solely obtained as light yellow solid. Presumably, it had similar structure of azafuloranthenes which was isolated from same plants family along with



Scheme 12. Methoxy group substitution of chlorinated tropones

tropoloisoquinolines. It is probably the result of retro-rearrangement to phenyl ring after the attack of methoxide or hydroxide to carbonyl group with the loss of chlorine moiety. On the other hand, when it was exposed to the in-situ generated magnesium methoxide, methoxy group successfully replaced the chlorine group.[14] The same result was obtained with commercially available magnesium methoxide. Consequentially, the **1da** isomer was converted to **1dc** which is one of the naturally occurring trpoloisoquinolins, isoimerubrine. The other isomer **1db** was also well transformed to **1dd** under same reaction condition in moderate yield (Scheme 12). Interestingly, different from direct basic hydrolysis with sodium hydroxide of chlorotropone, acidic hydrolysis of obtained methoxy substituted tropone gave desired hydroxy substituted tropone. It was confirmed by re-methylation with TMS dizaomethane which afforded methoxy tropone again along with some other kinds of isomer.

For indirect structure confirmation for obtained 1**da**, especially for the position of chlorine, the NMR spectroscpopy of obtained **1dc** was compared to the reported result of isoimerubrine. The NMR sepectroscopy was consistent with the literature of isoimerubrine, suggesting that the chlorine existed at C13 position. This result verified not only exact structure of **1dc** but also feasibility of its further functionalization. Additionally, X-ray

crystallography analysis was conducted with the other unnatural isomer **1dd** which was obtained as needle like red crystal after recrystallization to more precisely determine the position of chlorine. The result is shown below in figure 5.

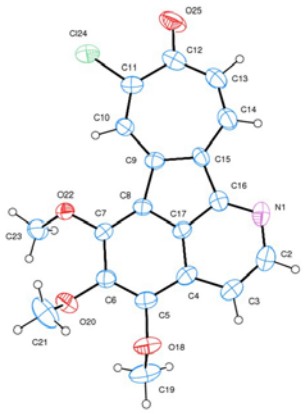


Figure 5. X-ray crystal structure compound **1db**

Conclusion

The convergent and divergent synthesis of pareitropone and its analogs has been accomplished in more concise and efficient manner using commercially available isoquinoline compounds. The reaction efficiency was highly improved to afford pareitropone with increased yield even under the shorter reaction scheme of 5 steps than the previously reported result. Furthermore, wide reaction scope of the new strategy enables us to synthesize another various tropoloisoquinoline compounds including naturally occurring isoimerubrine in good yield within 7 steps. Although chlorinated analogs were obtained as an isomeric mixture, since each structure was precisely confirmed, it should be useful to demonstrate the effect of tropone moiety by SAR studies.

Experimental Details

General remarks Unless otherwise noted, materials were obtained from commercial sources and were used without further purification. All glassware, syringes, needles, and magnetic stirring bars used in moisture-sensitive reactions were oven-dried and stored in desiccators prior to use. All moisture- or oxygen-sensitive reactions were conducted under an atmosphere of nitrogen. Upon work-up, solvents were evaporated by using a rotary evaporator. All solvents were purified prior to use. Ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. IR spectra were obtained on a commercially available ATR-FTIR spectrometer. NMR spectra were measured on commercially available spectrometers (^1H at 400 and ^{13}C at 100 MHz) in $CDCl_3$ unless stated otherwise and the data were reported as follows in ppm(δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, coupling constant in Hz, integration). Low and high resolution mass spectra were measured by the EI or FAB ionization method. Melting points were determined with an open capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed by using Merck 60 F_{254} glass plates pre-coated with a 0.25-mm thickness of silica gel under UV light (254 nm, 365 nm,) followed

by visualization with a phosphomolybdic acid staining solution or I_2. Column chromatography was performed on kiesel gel 60 (70-230 mesh) silica gel. Unless otherwise noted, all compounds purified by chromatography were sufficiently pure (>95%) by ^{1}H NMR analysis.

Crystallographic data for the structures reported here have been deposited with CCDC. (Deposition No. CCDC-1020424 **1db**) These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures-beta/ or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, E-mail: deposit@ccdc.cam.ac.uk.

4a: To a solution of **2a** (0.164 g, 0.788 mmol) and 4-(triisopropylsilyloxy)phenylboronic acid (0.696 g, 2.37 mmol) in THF (14 mL) and 2 M aqueous Na_2CO_3 (7 mL) was added at room temperature $Pd(PPh_3)_4$ (0.0455 g, 0.0394 mmol). The reaction mixture was heated at reflux for 5 h, cooled to room temperature, and was quenched by the addition of brine (20 mL). The mixture was extracted with ether (2 x 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (4:1 hexane–EtOAc) afforded **5a** (0.271 g, 91%) as an ivory solid: mp 60 °C; IR 3052, 2943, 2865, 1604, 1509 cm^{-1}; ^{1}H NMR δ1.16 (d, *J*=7.2, 18H), 1.32 (m,

3H), 7.02 (d, *J* = 8, 2H), 7.37 (d, *J* = 8, 2H), 7.51 (d, *J* = 6.4, 1H), 7.68 (d, *J* = 5.2, 1H), 7.71(d, *J* = 7.6, 1H), 7.79 (d, *J* = 8, 1H), 9.33 (s, 1H); ^{13}C NMR δ 12.8, 18.0, 120.0, 120.5, 125.6, 126.9, 128.1. 129.9, 131.1, 131.3, 136.3, 141.0, 142.8, 151.4, 156.1; HRMS (EI) $[M]^+$ calcd for $C_{24}H_{31}NOSi$ 377.2175 found 377.2171

4b: Above procedure for **4a** was followed with **2b** (0.353 g, 1.84 mmol) afforded **4b** (0.519 g, 86%) as a yellow syrup: IR 3042, 2944, 2866, 1599, 1509 cm^{-1}; ^{1}H NMR δ 1.17 (d, *J* = 7.2 Hz, 18H), 1.32 (m, 3H), 3.85 (s, 3H), 7.02 (d and m, *J* = 8.8 Hz, 2H), 7.25 (d and m, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 5.6 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR δ 12.7, 18.0, 57.0, 118.5, 119.8, 119.9, 126.0, 126.6. 127.4, 128.9, 132.0, 140.5, 150.8, 154.5, 155.7; HRMS (EI) $[M]^+$ calcd for $C_{25}H_{33}NO_2Si$ 407.2280, found 407.2284

4c: Above procedure for **4a** was followed with **2c** (0.100 g, 0.97 mmol) afforded **4c** (0.134 g, 83%) as a yellow crystal: mp 99 ºC IR 3217, 2936, 1615, 1557 cm^{-1}; ^{1}H NMR δ 1.15 (d, J = 7.2, 18H), 1.28-1.36 (m, 3H), 3.58 (s, 3H), 4.02 (s, 3H), 8.80 (m, 2H), 7.11 (s, 1H), 7.27 (m, 2H), 7.53 (dd, *J* = 0.4, 5.6, 1H), 8.41 (d, *J* = 5.6, 1H), 8.85 (s, 1H); ^{13}C NMR δ 12.7, 17.9,

55.9, 60.8, 104.6, 119.2, 119.9, 124.2, 126.3, 131.7, 132.6, 134.5, 142.5, 147.3, 150.6, 155.9; HRMS (EI) $[M]^+$ calcd for $C_{26}H_{35}NO_3Si$ 437.2386, found 437.2390

4d: Above procedure for **4a** was followed with **2d** (0.125 g, 0.419 mmol) to afforded **4d** (0.178 g, 91%) as a pale yellow syrup: IR 3036, 2944, 2867, 1601, 1501 cm^{-1}; ^1H NMR δ 1.15 (s, 18H), 1.27-1.36 (m, 3H), 3.63 (s, 3H), 4.08 (s, 3H), 4.09 (s, 3H), 7.09 (m, 2H), 7.26 (m, 3H), 7.88 (apparent d, *J* = 5.6, 1H), 8.44 (d, *J* = 5.6, 1H), 8.91 (s, 1H); ^{13}C NMR δ 12.7, 18.0, 61.2, 61.3, 61.6, 114.2, 119.9, 125.1, 126.4, 128.3, 129.3, 131.9, 1422.1, 146.1, 147.2, 150.5, 151.0, 155.9 HRMS (EI) $[M]^+$ calcd for $C_{27}H_{37}NO_4Si$ 467.2492, found 467.2499

7c: Above procedure for **4a** was followed with **2c** (0.512 g, 1.94 mmol) to afforded **7c** (0.760 g, 83%) as a pale yellow syrup: IR 3053, 2946, 2867, 1613, 1498 cm^{-1}; ^1H NMR δ 1.18 (d, *J* = 7.2, 18H), 1.402-1.346 (m, 3H), 3.62 (s, 3H), 4.05 (s, 3H), 7.05 (d, *J* = 8.4, 1H), 7.13 (s, 1H), 7.19 (dd, *J* = 2.0, 8.4), 7.42 (d, *J* = 2.0, 1H), 7.54 (d, *J* = 5.4, 1H), 8.42 (d, *J* = 5.4, 1H), 8.83 (s, 1H); ^{13}C NMR δ 13.0, 18.0, 55.9, 61.0, 105.1, 119.3, 120.0, 123.9, 125.3, 127.3, 129.8, 131.2, 132.3, 134.5, 142.7, 147.3, 149.9, 151.8, 155.8

HRMS (FAB) $[M+H]^+$ calcd for $C_{26}H_{35}ClNO_3Si$ 472.2075, found 472.2073

7d: Above procedure for **4a** was followed with **2d** (0.149 g, 1.28 mmol) to afforded **7d** (0.382 g, 89%) as an ivory solid: mp 63 ^oC; IR 3032, 2944, 2866, 1602, 1450, 1458 cm^{-1}; ^1H NMR δ 1.18 (d, *J* = 7.2, 18H), 1.13-1.40 (m, 3H), 3.67 (s, 3H), 4.07 (s, 3H), 4.09 (s, 3H), 7.04 (d, *J* = 8.0, 1H), 7.14 (dd, *J* = 2.0, 8.4, 1H), 7.41 (d, *J* = 2.0, 1H), 8.38 (dd, *J* = 5.6, 0.8, 1H), 8.45 (d, *J* = 5.6, 1H), 8.89 (d, *J* = 0.8, 1H); ^{13}C NMR δ 13.0, 18.0, 61.3, 61.3, 61.6, 114.3, 119.9, 124.8, 125.3, 126.8, 127.3,129.4, 130.0, 132.5, 142.2, 146.4, 147.1, 150.1, 151.1, 151.7 HRMS (FAB) $[M+H]^+$ calcd for $C_{27}H_{37}ClNO_4Si$ 502.2180, found 502.2178

6a: To a solution of **4a** (0.525 g, 1.39 mmol) in $CHCl_3$ (0.5 mL) and $MeNO_2$ (6.0 mL) in the dark was added at room temperature 3-butyn-2-one (0.12 ml, 1.67 mmol). The reaction mixture was stirred overnight, quenched with water (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (2:1 hexane–EtOAc) afforded compound **5a** (0.653 g, 93%) as a yellow liquid. Then $TBAF{\cdot}3H_2O$ (0.249 g, 0.789 mmol) was added at room temperature to a solution of **5a** (0.200 g,

0.395 mmol) in THF (10 mL) in the dark. The reaction mixture was stirred for 1 h, quenched with saturated aqueous NH_4Cl (15 mL) and brine (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:2 hexane–EtOAc) afforded compound **6a** (0.115 g, 83%) as a pale yellow solid: mp 199 ºC; IR 3131, 2015, 1644, 1539 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.06 (s, 3H), 4.34 (dd, *J* = 3.6, 11.8, 1H), 4.55 (apparent t, *J* = 11.8, 1H), 5.44 (br s, 1H), 5.75 (br s, 1H), 6.24 (d, *J* = 7.2, 1H), 6.91 (m, 3H), 7.12 (d, *J*=7.2, 1H), 7.21 (m, 3H), 7.38 (apparent t, *J* = 7.6, 1H), 7.44 (br s, 1H), 9.67 (s, 1H); ^{13}C NMR δ 27.7, 75.3, 103.2, 110.3, 116.1, 123.6, 124.6, 129.3, 129.5, 130.4, 131.5, 140.2, 147.7, 157.6, 159.4; HRMS (EI) $[M]^+$ calcd for $C_{20}H_{18}N_2O_4$ 350.1266, found 350.1265

6b: Above procedure for **6a** was followed with **4b** (0.591 mg, 1.27 mmol) to afford compound **6b** (86% in 2 steps) as a yellow solid: mp 155 ºC; IR 3647, 2949, 1651, 1553 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.03 (s, 3 H), 3.67 (s, 3 H), 4.30 (dd, *J* = 11.4, 3.2, 1 H), 4.53 (t, *J* = 11.4, 1 H), 5.40 (br s, 2 H), 6.22 (d, *J* = 7.2, 1 H), 6.73 (d, *J* = 7.2, 1 H), 6.91 (apparently d and t, *J* = 8.4, 2.4, 2 H), 7.07 (d, *J* = 8.3, 1 H), 7.24 (apparently q, *J* = 8.3, 3 H), 7.33 (br s, 1 H), 9.64 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.3, 55.7, 74.8, 102.1,

110.3, 111.7, 115.6, 115.7, 123.4, 124.5, 125.5, 126.0, 128.4, 130.3, 131.3, 147.5, 156.7, 156.9, 194.9; HRMS (EI) $[M]^+$ calcd for $C_{21}H_{20}N_2O_5$ 380.1372, found 380.1376

6c: Above procedure for **6a** was followed with **4c** (0.566 g, 1.29 mmol) to afford compound **6c** (86% in 2 steps) as a yellow solid: mp 153.5 ºC; IR 3217 2936, 1615, 1557 cm^{-1}; ^1H NMR δ 2.16 (s, 3H), 3.53 (s, 3H), 3.91 (s, 3H), 3.95 (dd, *J* = 3.6, 12, 1H), 4.51 (apparent t, J = 10.8, 1H), 5.42 (br s, 1H), 5.49 (d, J=13.2, 1H), 5.42 (br s, 1H), 5.97 (br s,1H), 6.09 (d, *J* = 7.4, 1H), 6.44 (d, *J* = 7.4, 1H), 7.13 (m, 4H), 7.28 (m, 1H); ^{13}C NMR δ 28.5 56.0, 60.9, 74.2, 102.4, 108.7, 116.2, 116.3, 125.7, 127.0, 123.0, 131.0, 134.4, 147.0, 147.1, 153.4, 156.2, 196.8; HRMS (FAB) $[M+H]^+$ calcd for $C_{22}H_{22}N_2O_6$ 411.1556, found 411.1560

6d: Above procedure for **6a** was followed with **4d** (0.095 g, 0.203 mmol) to afford compound **6d** (81% in 2 steps) as a yellow solid: mp 185 ºC; IR 3164, 2938, 1649, 1613, 1557 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.02 (s, 3H), 3.33 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.27 (dd, *J* = 12.4, 3.2, 1H), 4.56 (apparent t, *J* = 10.8, 1H), 5.34 (br s, 1H), 6.30 (d, *J* = 7.6, 1H), 6.83 (d, *J* = 7.6, 1H), 6.90 (m, 2H), 7.12 (m, 1H), 7.34 (br s, 1H), 9.65 (s, 1H) ^{13}C NMR δ 27.7,

61.1, 61.2, 61.7, 75.2, 103.0, 104.9, 116.0, 104.9, 116.0, 116.1, 120.9, 124.6, 130.5, 130.7, 131.6, 146.6, 147.6, 147.7, 151.5, 157.5, 195.3; HRMS (EI) $[M]^+$ calcd for $C_{23}H_{24}N_2O_7$ 440.1583, found 440.1586

9c: Above procedure for **6a** was followed with **7c** (0.273 g, 0.482 mmol) to afford compound **9c** (77% in 2 steps) as a yellow solid: mp 114 ºC; IR 3084, 2937, 1609, 1552 cm^{-1}; ^1H NMR δ 2.15 (apparent d, *J* = 2.8, 3H), 3.55 (apparent d, *J* = 6.8, 3H), 3.91 (s, 3H), 4.00 (m, 1H), 4.51 (m, 1H), 5.42 (br s, 1H), 5.48 (dd, *J* = 10, 3.6, 1H), 6.07 (d and br s, *J* = 7.6, 2H), 6.44 (d, *J* = 7.6, 1H), 6.73 (s, 1H), 7.09 (m, 1H), 7.22 (m, 3H); ^{13}C NMR δ 28.4, 28.6, 56.0, 61.0, 61.0, 74.3, 102.5, 109.0, 109.1, 111.0. 111.3, 116.9, 117.1, 117.2, 120.8, 120.9, 126.6, 126.8, 127.1, 127.2, 128.7, 129.6, 129.7, 130.6, 132.9, 133.0, 146.9, 147.1, 152.1, 152.1, 153.5, 196.8, 196.9; HRMS (FAB) $[M+H]^+$ calcd for $C_{22}H_{22}ClN_2O_6$ 445.1166, found 445.1161

9d: Above procedure for **6a** was followed with **7d** (1.11 g, 2.22 mmol) to afford compound **9d** (77% in 2 steps) as a deep yellow solid: mp 140 ºC; IR 3101, 2940, 1610, 1554 cm^{-1}; ^1H NMR δ 2.16 (apparent d, J=1.2, 3H), 3.61 (apparent d, J=9.2, 3H), 3.94 (s, 3H), 4.00 (m, 1H), 4.56(m, 1H), 5.41(br s, 1H), 5.49 (dd, *J* = 7.2, 13.6, 1H), 6.43 (m, 1H), 7.01 (m, 1H), 7.22 (m, 4H);

^{13}C NMR δ 28.5, 28.6, 60.9, 61.0, 61.3, 61.3, 61.5, 74.0, 74.1, 102.6, 106.1, 117.0, 117.2, 120.3, 120.8, 120.8, 120.8, 126.5, 126.8, 128.2, 128.4, 129.0, 129.8, 130.7, 146.6, 146.7, 146.9, 148.6, 151.8, 151.9, 152.0, 196.6, 196.7; HRMS (FAB) $[M+H]^+$ calcd for $C_{23}H_{24}ClN_2O_7$ 475.1272, found 475.1267

1a: The phenol **6a** (70 mg, 0.200 mmol) was dissolved in 1.0 M aqueous KOH (1.6 mL) and then diluted with H_2O (3.2 mL), which was subjected to a solution of $K_3Fe(CN)_6$ (0.400 mmol) in $CHCl_3$ (8 mL) and H_2O (8 mL) solution over 10 min at 0 ºC. After additional 30 min, DDQ (0.200 mmol) was added and vigorously stirred for an hour. It was quenched by saturated Na_2SO_3 solution (5 mL) and $NaHCO_3$ solution (5 mL) and extracted by $CHCl_3$ (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dried under vacuum and subjected to the next reaction without further purification. To a solution of the crude product (spirocyclic nitroolefin) in THF (2 mL) was added 1.0 M Me_2NH solution in MeOH (2 mL). The reaction was completed in 30 min and it was concentrated *in vacuo*. To a solution of the crude product in THF (5 mL) was added triflic anhydride (0.600 mmol) in drops at 0 ºC under N_2 in the dark. The reaction was completed in 10 min. The reaction mixture was quenched by saturated $NaHCO_3$ solution to pH 8, extracted with $CHCl_3$ (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and

concentrated in vacuo. Purification by column chromatography (20:1 CH_2Cl_2–MeOH) afforded **1a** (52% in 3 steps) as a reddish solid: mp 194 °C; IR 2924, 1599, 1574, 1553 cm^{-1}; ^1H NMR δ 7.26 (m, 2H), 7.71 (d, *J* = 5.8, 1H), 7.79 (d, *J* = 6.8, 1H), 7.81 (d, *J* = 7.2, 1H), 7.83 (m, 1H), 7.93 (d, *J* = 7.2, 1H), 7.97(d, *J* = 6.8, 1H), 8.20 (m, 1H), 8.84 (d, *J* = 5.8, 1H); ^{13}C NMR δ 120.2, 122.6, 124.1, 129.1, 130.0, 130.2, 131.7, 132.6, 137.3, 141.1, 121.1, 141.8, 143.3, 147.4, 160.4, 187.7; HRMS (EI) $[M]^+$ calcd for $C_{16}H_9NO$ 231.0684, found 231.0682

1b: Above procedure for **1a** (38 mg, 0.100 mmol) was followed with **6b** to afford compound **1b** (19 mg, 73% in 3 steps) as a reddish solid: mp 245 °C; IR 2919, 1614, 1597 cm^{-1}; ^1H NMR (300 MHz) δ 4.22 (s, 3 H), 7.23 (d, *J* = 11.6, 2 H), 7.67 (d, *J* = 5.6, 1 H), 7.51 (d, *J* = 8.8, 1 H), 8.14 (d, *J* = 8.8, 1 H), 8.27 (d, *J* = 11.6, 1 H), 8.37 (d, *J* = 11.6, 1 H), 8.80 (d, *J* = 5.6, 1 H); ^{13}C NMR (75 MHz) δ 56.5, 119.4, 120.2, 124.1, 127.1, 130.5, 133.0, 133.8, 138.9, 139.6, 141.3, 143.4, 145.6, 158.2, 158.6, 188.2; HRMS (EI) $[M]^+$ calcd for $C_{17}H_{11}NO_2$, 261.0790; found 261.0789.

1c: Above procedure for **1a** (62 mg, 0.151 mmol) was followed with **6c** to afford compound **1c** (33 mg, 75% in 3 steps) as an orange solid: mp 215 °C;

IR 2950, 1605, 1577 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.06 (s, 3 H), 4.19 (s, 3 H), 7.12 (s, 1 H), 7.16 (dd, *J* = 12.0, 2.8, 1 H), 7.19 (dd, *J* = 12.0, 2.8, 1 H), 7.51 (d, *J* = 5.6, 1 H), 8.13 (d, *J* = 12.0, 1 H), 8.21 (d, *J* = 12.0, 1 H), 8.69 (d, *J* = 5.6, 1 H); ^{13}C NMR (75 MHz) δ 56.6, 62.1, 107.5, 118.7, 119.8, 125.1, 129.5, 130.3, 133.1, 140.7, 141.3, 141.4, 142.2, 146.7, 151.5, 157.5, 158.9, 188.0; HRMS (EI) $[M]^{+}$ calcd for $C_{18}H_{13}NO_3$ 291.0895, found 291.0895

1d: Above procedure for **1a** was followed with **6d** (0.044 g, 0.100 mmol) to afford compound **1d** (72% in 3 steps) as a reddish solid: mp 183 ºC; IR 2938, 1629, 1605, 1577, 1553 cm^{-1}; ^{1}H NMR δ 4.01 (s, 3H), 4.22 (s, 3H), 4.24 (s, 3H), 7.16 (m, 2H), 7.77 (d, *J* = 5.6, 1H), 8.15 (d, *J* = 12. 1H), 8.21 (d, *J* = 12, 1H), 8.74 (d, *J* = 5.6, 1H); ^{13}C NMR δ 61.5, 62.1, 62.1, 115.5, 120.0, 120.3, 125.4, 130.3, 132.8, 139.4, 139.7, 141.6, 142.8, 154.9, 148.8, 153.1, 156.2, 158.1, 188.0; HRMS (EI) $[M]^{+}$ calcd for $C_{19}H_{15}NO_4$ 321.1001, found 321.0996

1ca / 1cb: The phenol **9a** (0.120 g, 0.270 mmol) was dissolved in 1.0 M aqueous CsOH (0.8 mL) and then diluted with H_2O (3.2 mL), which was subjected to a solution of $K_3Fe(CN)_6$ (0.400 mmol) in $CHCl_3$ (4 mL) and H_2O (4 mL) solution over 10 min at 0 ºC. After additional 1 h, DDQ (0.200

mmol) was added and vigorously stirred for an hour. It was quenched by solid Na_2SO_3 and extracted by $CHCl_3$ (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Then it was treated once again with DDQ (0.200 mmol). After additional 1 h, it was quenched by saturated $NaHCO_3$ solution (5 mL) and extracted by $CHCl_3$ (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dried under vacuum and subjected to the next reaction without further purification. To a solution of the crude product (spirocyclic nitroolefin) in THF (2 mL) was added 1.0 M Me_2NH solution in MeOH (2 mL). The reaction was completed in 1 h and it was concentrated *in vacuo*. To a solution of the crude product in THF (5 mL) was added triflic anhydride (0.600 mmol) in drops at room temperature under N_2 in the dark. The reaction was completed in an hour. The reaction mixture was quenched by saturated $NaHCO_3$ solution to pH 8, extracted with $CHCl_3$ (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (20:1 CH_2Cl_2–MeOH) afforded a mixture of **1ca** and **1cb** (69% in 3 steps, **1ca** : **1cb** = 1:2) as an orange solid. The regio-isomeric mixture was separated by preparative TLC (20:1 CH_2Cl_2–MeOH). For **1ca:** mp 194 ^oC; IR 2944, 1597, 1578 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 4.01 (s, 3H), 4.21 (s, 3H), 7.22 (s, 1H), 7. 30

(d, *J* = 12, 1H), 7.56 (d, *J* = 5.8, 1H), 8.27 (d, *J* = 12, 1H), 8.72 (d, *J* = 5.8, 1H), 8.77 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 57.1, 62.6, 108.5, 119.5, 120.5, 124.8, 130.1, 130.2, 132.8, 138.4, 138.5, 141.9, 147.3, 147.6, 152.5, 127.1, 159.6, 180.1; HRMS (FAB) $[M+H]^+$ calcd for $C_{18}H_{13}ClNO_3$ 326.0584, found 326.0585; For **1cb:** mp 198 ºC; IR 2958, 1605, 1584 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 4.07 (s, 3H), 7.24 (s, 3H), 7.23 (s, 1H), 7.33 (d, *J* = 12.2, 1H), 7.61 (d, *J* = 5.6, 1H), 8.23 (d, *J* = 12.2, 1H), 8.73 (d, *J* = 5.6, 1H), 8.98 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 57.2, 62.8, 108.6, 119.5, 120.7, 124.8, 130.0, 130.2, 133.4, 137.9, 139.5, 141.3, 147.5, 148.6, 152.5, 157.6, 159.6, 180.3; HRMS (FAB) $[M+H]^+$ calcd for $C_{18}H_{13}ClNO_3$ 326.0584, found 326.05853

1da / 1db: Above procedure for **1ca/1cb** was followed with **9d** (0.064 g, 0.130 mmol) to afford a mixture of **1da** and **1db** (62% in 3 steps, **1da** : **1db** = 1:2) as a reddish solid. The regio-isomeric mixture was separated by preparative TLC (20:1 CH_2Cl_2–MeOH). For **1da:** mp 191 ºC; IR 2943, 1601, 1579 cm^{-1}; ^{1}H NMR δ 4.01 (s, 3H), 4.23 (s, 3H), 4.27 (s, 3H), 7.41 (d, *J* = 12.2, 1H), 7.62 (d, *J* = 5.8, 1H), 8.29 (d, *J* = 12.2, 1H), 8.53 (d, *J* = 5.8, 1H), 8.85 (s, 1H); ^{13}C NMR δ 61.5, 62.1(3C), 115.8, 119.5, 120.1, 125.4, 129.9, 132.0, 136.4, 138.3, 141.9, 145.8, 148.7, 153.5, 156.4, 157.0, 179.9; HRMS (FAB) $[M+H]^+$ calcd for $C_{19}H_{15}ClNO_4$ 356.0690, found 356.0686; For **1db:**

mp 193 ºC; IR 2950, 1607, 1572 cm^{-1}; ^{1}H NMR δ 4.02 (s, 3H), 4.24 (s, 3H), 4.29 (s, 3H), 7..35 (d, *J* = 12, 1H), 7.81 (d, *J* = 5.6, 1H), 8.24 (d, *J* = 12, 1H), 8.77 (d, *J* = 5.6, 1H), 8.93 (s, 1H); ^{13}C NMR δ 61.6, 62.2, 62.2, 115.8, 119.3, 120.2, 120.2, 125.4, 129.5, 132.5, 135.9, 138.9, 139.5, 146.0, 148.4, 148.6, 153.6, 156.4, 157.2, 179.8; HRMS (FAB) $[M+H]^{+}$ calcd for $C_{19}H_{15}ClNO_4$ 356.0690, found 356.0688

1dc: The magnesium metal (29 mg, 1.20 mmol) was added to a flame dried two-neck round-bottom flask. Dry methanol and three crystals of iodine were added to the flask, then refluxed for 1 h. During the reaction, magnesium metal had been dissolved. The precursor **1da** (15 mg, 0.04 mmol) was dissolved in methanol (10 ml) and added to the in situ generated magnesium methoxide. Then the reaction was proceeded at room temperature for 12 h. The reaction was quenched by water and diluted with chloroform (30 ml). The layers were separated and the aqueous layer extracted with chloroform (2 x 30 ml). The combined organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (20:1 CH_2Cl_2–MeOH) afforded compound **1dc** (6 mg, 43 %) as a reddish solid: mp 186 ºC; IR 2947, 1601, 1582, 1548 cm^{-1}; ^{1}H NMR δ 4.03 (s, 3H), 4.19 (s, 3H), 4.19 (s, 3H), 4.21 (s, 3H), 7.41 (d, *J* = 12,

1H), 7.80 (d, *J* = 6, 1H) 7.92 (s, 1H) 8.28 (d, *J* = 12, 1H) 8.74 (d, *J* = 6, 1H); ^{13}C NMR δ 56.8, 61.4, 61.9, 62.1, 106.7, 115.7, 120.9, 121.1, 125.6, 132.5, 136.4, 136.8, 139.0, 145.4, 149.4, 151.2, 154.3, 158.5, 164.3, 180.1; HRMS (FAB) $[M+H]^+$ calcd for $C_{20}H_{18}NO_5$ 352.1185, found 352.1186

1dc: Above procedure for **1dc** was followed with **1db** (11 mg, 0.03 mmol) to afford compound **1dd** (6 mg, 70 %) as an orange solid: mp 184 ºC; IR 2942, 1600, 1581, 1548 cm^{-1}; ^{1}H NMR δ 4.04 (s, 3H), 4.12 (s, 3H), 4.22 (s, 3H), 4.27 (s, 3H), 7.31 (d, *J* = 12, 1H), 7.69 (d, *J* = 5.6, 1H), 8.02 (s, 1H), 8.18 (d, *J* = 12, 1H), 8.67 (d, *J* = 5.6, 1H); ^{13}C NMR δ 56.4, 61.5, 61.7, 62.1, 109.6, 114.2, 120.4, 121.0, 125.1, 129.8, 134.1, 134.5, 142.2, 145.5, 148.8, 152.9, 155.2, 158.8, 165.6, 180.1; HRMS (FAB) $[M+H]^+$ calcd for $C_{20}H_{18}NO_5$ 352.1185, found 352.1179

Chapter II

Process development of bio-based adipic acid from galactose

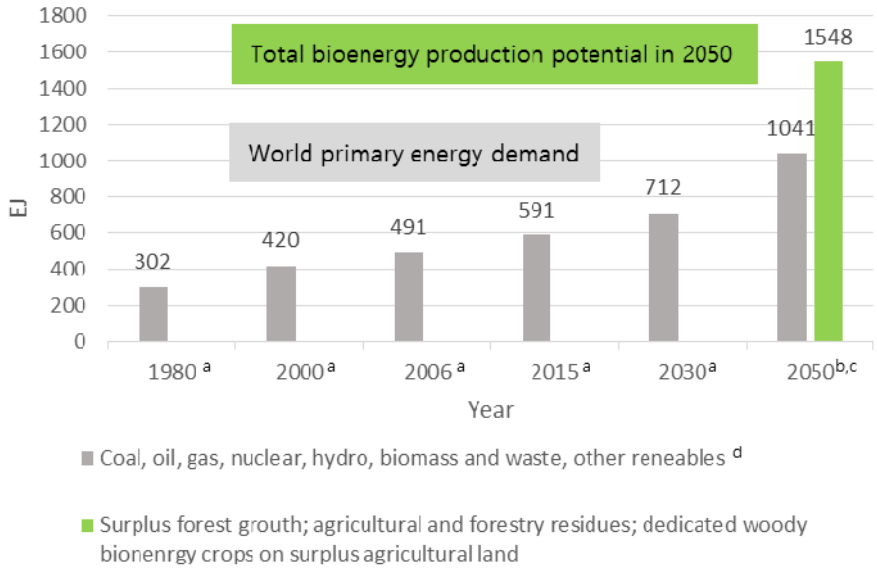
Introduction

1. Global research trend in biomass

Recent global energy issues, such as higher energy demands and price, depletion of source, environmental crisis have made a new green wave, an effort to find eco-friend and sustainable alternatives energy, across the research, business, industry and politics areas. Regarding these matters, plenty of studies have been made and it was concluded that biomass is the next-generation energy source that could replace current energy source of petroleum. In this perspectives, over the year to come, global biomass demands are expected to rapidly grow in the bio-power, bio-fuels, and bio-based products and the needs will be increasing by 70~110 percent to meet demand in 2050 (Figure 6).[15]

Biomass is organic materials derived from living, or recently living organisms. It most often refers to plants or plant-based material that are no

used for food or feed, and are specifically called lignocelloulosic biomass.[16] Due to its abundance, the fourth largest energy source after coal, oil, and natural gas, and energy potential, biomass is considered as most possible and important alternative to petroleum. In this perspectives, a lot of intensive research have been made and further study is required for conversion of the biomass into biofuel or value-added biomaterials.



Notes: [a] IEA, 2008

[b] Highest consumption scenario (Smmts et al., 2004)

[c] Based on scenario 4 in the source, where a type of agricultural management applied is similar to the best available technology in the industrialized regions (Smeets et al., 2006)

[d] Includes traditional and modern uses

Figure 6. World primary energy demand and forecasts [15d]

2. Bio-based adipic acid

Adipic acid is one of the high demand commodity chemical currently produced from petroleum resources across manufacturing industry. Its primary application is in the production of nylon 66 polyamide which is one of the important plastics in synthetic fiber industry. The secondary application is the usage as its esters in plasticizers, lubricants, and a variety of polyurethane resins. Among those esters, its butyl ester form of dibutyl adipate is commercialized under a name of Cetiol®B (BASF), and it is used as a fast spreading emollient for all cosmetic applications, mostly sun-care formulation. Adipic acid is also added to gelatins and jams as an acidulant, and to other foods as a buffering or neutralizing agent. Other miscellaneous applications are in the adhesives, insecticide, tanning, dying, and textile industries. With these wide usefulness, the global market for adipic acid was valued at $6.4 billion in 2014 and expected to increase to $7.7 billion by 2020 at a compound annual growth rate (CAGR) of 3.2% (Fiqure 7). [17]

Currently, the commercial adipic acid is prepared via nitric acid oxidation of cyclohexanol, cyclohexanone, or a mixture of these two called ketone-alcohol (KA) oil derived from benzene, the most representative petro chemicals. However, petroleum-based process closely depends on the depletion of petroleum resources, and current process using nitric acid cause

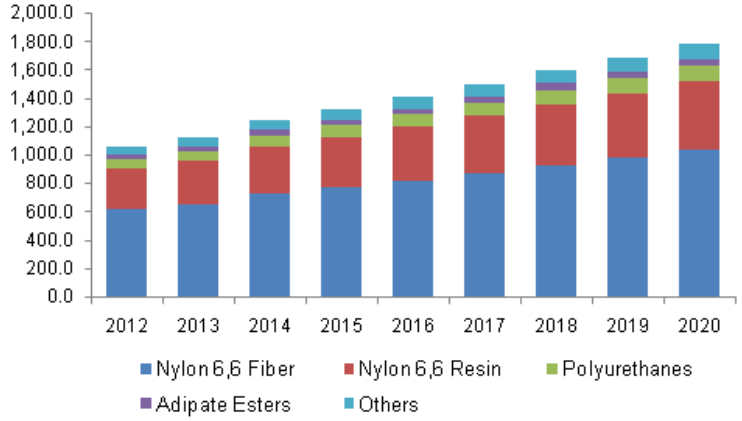
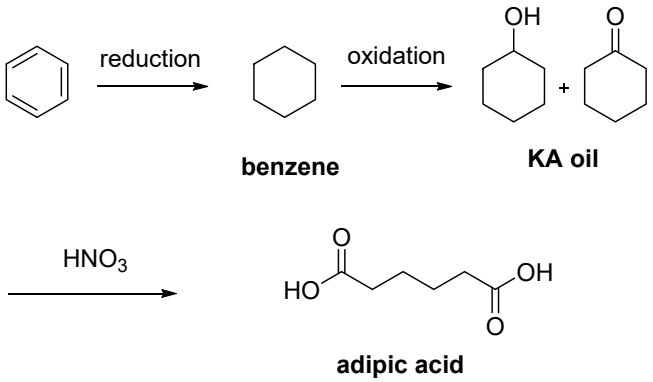


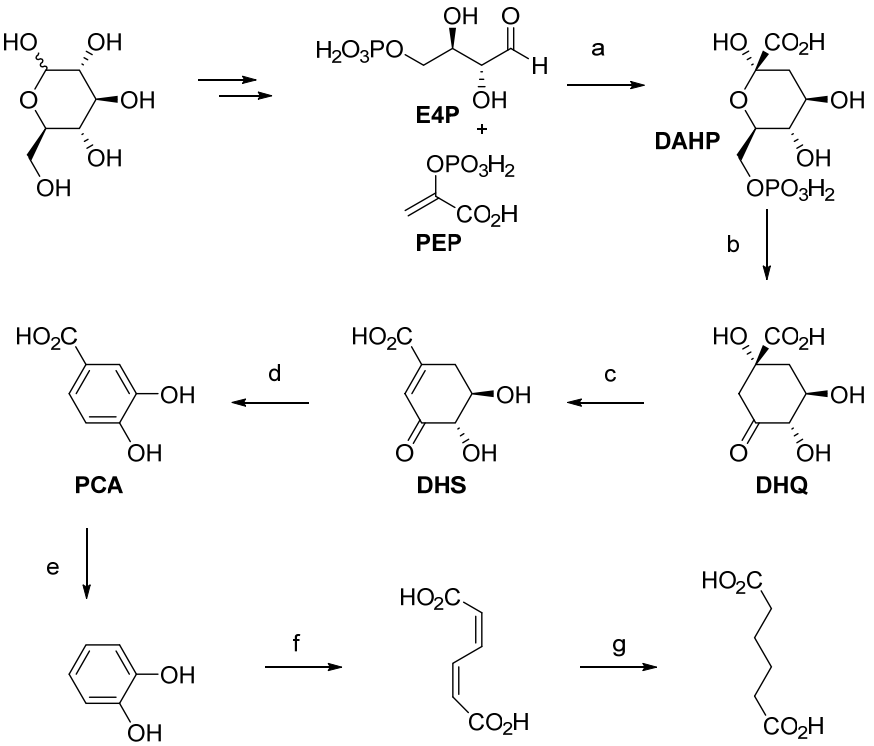
Figure 7. North america adipic acid market revenue by product, 2012-2020 (USD Million)[17b]

significant environmental problem by emitting large amount of NO_x, major harmful substance (Scheme 13). Therefore, with worldwide caution for the depletion of petroleum resources and environmental problem, research for bio-based adipic acid has attracted many attentions of scientists and researchers because it should have a great ripple effect across the manufacturing industry with its high demands and wide applications. These efforts to prepare new paradigm shift from fossil fuel to biomass are consistent with the new global research trend in manufacturing and energy industry. Moreover, much milder process could be introduced by altering the source of adipic acid from petroleum resources to sugar. The use of sugar would provide more reliable adipic acid in terms of safety and health particularly for cosmetic and food industries.



Scheme 13. Current adipic acid production using nitric acid

In the same context, several attempts have recently been made to develop synthetic process for adipic acid from hexose in both ways of chemical and biological catalytic conversion. In terms of bio-catalytic process, Frost et al. successfully produced adipic acid using *cis,cis*-muconic acid which was produced by fermentation using *Escherichia coli* (Scheme 14).[18] However, the complex fermentation process using various enzyme on each step and low productivity were not appropriate to industrial process. In order to break through the limitation of biological conversion, a chemical catalytic conversion have also been achieved. Firstly, Rennovia Inc. accomplished direct reduction process using hydrohalic acid and metal catalyst under hydrogenation condition.[18] Secondly, adipic acid synthesis was successfully conducted by Toste *et al*. and Zhang *et al*. employing deoxydehydration (DODH) reaction.[19j,k]



Scheme 14. Synthesis of adipic acid from glucose by enzymatic conversion

Biosynthetic intermediates (abbreviations): D-erythrose 4-phosphate (E4P), phosphoenolpyruvic acid (PEP), 3-deoxy-D-*arabino*heptulosonic acid 7-phosphate (DAHP), 3-dehydroquinic acid (DHQ), 3-dehydroshikimic acid (DHS), protocatechuic acid (PCA). Enzymes (encoding genes) or reaction conditions: (a) DAHP synthase (*aroF*FBR), (b) 3-dehydroquinate synthase (*aroB*), (c) 3-dehydroquinate dehydratase (*aroD*), (d) DHS dehydratase (*aroZ*), (e) protocatechuate decarboxylase (*aroY*), (f) catechol 1,2-dioxygenase (*catA*), (g) 10% Pt/C, H_2, 3400 kPa, 25 °C

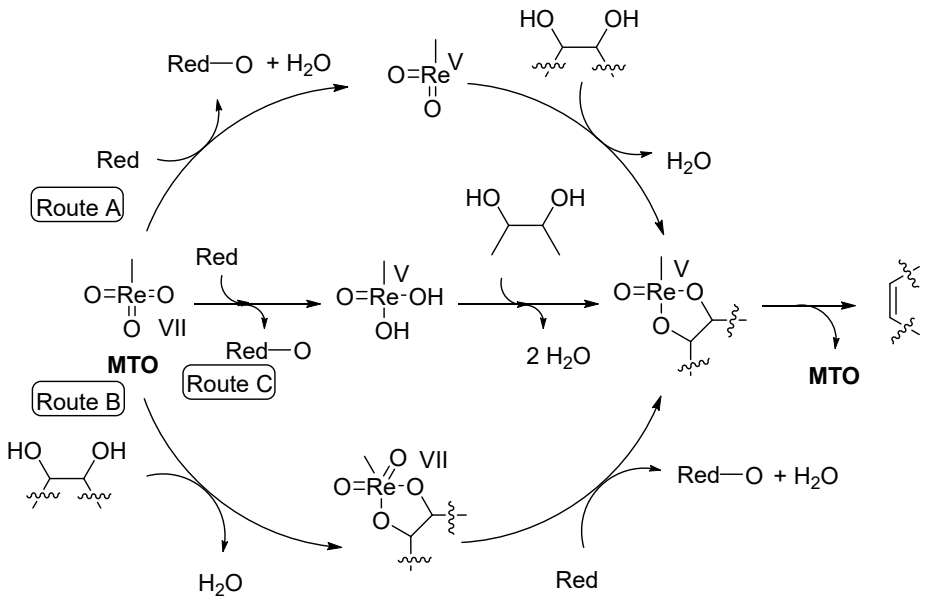
3. Deoxydehydration(DODH) reaction

Deoxydehydration (DODH) reaction has recently attracted much attention as one of the most promising method to remove rich oxygen content in biomass like carbohydrate and polyols to replace hydrocarbon based petrochemical. Therefore, this type of reaction has been intensively investigated by several groups to demonstrate mechanism and reaction scope.[19,20] Firstly, there have been many efforts to develop efficient catalysts and reducing agent such as sulfite, PPh_3, H_2 and alcohols. Concerning catalyst, rhenium based-catalysts, like MTO($MeReO_3$), Re_2O_7, $HReO_4$, and NH_4ReO_4, are most representative but it is relatively expensive and rare which is problematic in industrial perspective. Therefore, various metal catalysts having similar oxophilicity with rhenium, e.g. vanadium (V),[19m] molybdenum (Mo)[19n,o,p] and tungsten(W),[19p] were ever applied to develop cheaper and more abundant alternatives for rhenium catalysts.

Regarding mechanism, several computational mechanism studies have been accomplished, and the most possible three pathways were described in scheme 15.

Toste *et al.*[19j] explained that DODH is proceeded following sequence: 1) reduction of rhenium (VII) to rhenium (V), 2) condensation of vicinal diol, c) extrucsion of olefin. On the other hand, Abu-Omar group postulated[19q] the

reaction sequence of 3), 1) and c). In very recent, Wang *et al.*[19a] have proposed another new pathway C shown the scheme 15.



Scheme 15. Mechanistic consideration of DODH reaction

Result and Discussion

1. Efficient large scale one-pot process of bio-based adipic acid

1.1 Introduction

Although several results of adipic acid synthesis have been reported, those attempts are performed only in small laboratory scale which was inappropriate for the industrial process. Therefore, as an effort for industrialization of bio-based adipic acid, we practically extended reaction scale, and explored suitable reaction conditions and process for the mass production of adipic acid. For efficiency of C-O bond cleavage, deoxydehydration (DODH) reaction seems more promising in terms of scalability and efficiency. However, unfortunately, high efficiency of DODH reaction in small scale was not reproducible in large scale synthesis. Significantly low conversion as well as complex reaction and purification process were serious problems in large scale synthesis. Hence, we have developed a practical synthetic process favorable for the industrial production of bio-based adipic acid by applying milder and more efficient reaction condition and simplifying multiple step transformation and purifications in one-pot.

1.2 Result and Discussion

1.2.1 Adipic acid synthesis via DODH reaction from glucose

In order to synthesize adipic acid from sugar compound, glucose derived glucaric acid was firstly considered as starting material, because glucose is the most abundant C6 sugar. Glucaric acid was easily obtained from glucose by oxidation in its monopotassium salt after pH adjustmetn.[21]

However, DODH reaction did not occurred at all and it might due to the low solubility of glucaric acid slat. To enhance the solubility of glucaric acid, we tired neutralization into free acid using Amberlyst®15, and *in situ* esterification using various alcohol solvents, such as ethanol, isopropanol, 1-butanol, and 3-pentanol. However, in both of the cases, reaction efficiency was quite low because of cyclized lactone under acidic condition which is presumably due to a sickle-like(bent) structure of glucaric acid (Figure 8).[22]

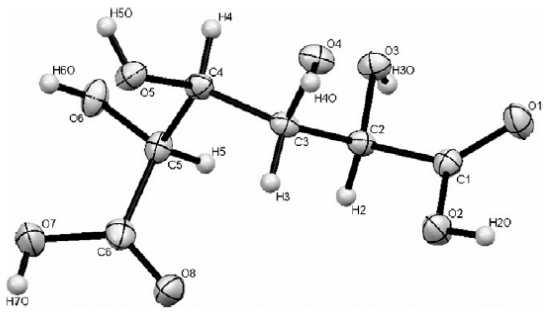
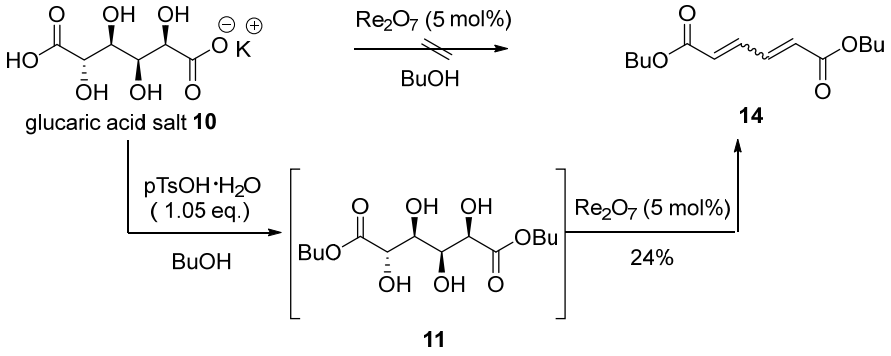


Figure 8. X-ray crystal structure of D-glucaric acid [22]

Because it is difficult to selectively isolate free acid from the mixture, DODH reaction was attempted without isolation in the presence of butanol reducing agent. As a result, the desired muconate was synthesized in maximum 24 % of yield as a mixture of *trans,trans*- and *cis,trans*-muconate (Scheme 16). Although we did not precisely check the efficiency of DODH reaction, it is known that it might because of the different energy level of transition state depending on relative stereochemistry of the diols.[19d,19e,19g,20b,]

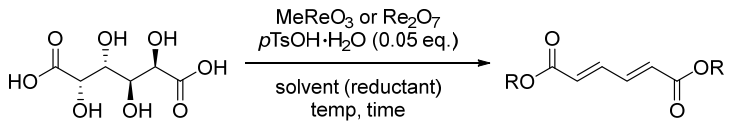


Scheme 16. DODH reaction of glucaric acid monopotassium salt

1.2.2 Adipic acid synthesis via DODH reaction from galactose

Due to the low DODH efficiency of glucaric acid, we have changed starting material to galactaric acid. Galactaric acid has two vicinal *anti* diol groups exist and it is readily obtainable as a free acid or ester form galactose by oxidation.[22] With altered staring material, DODH reaction have been explored to find optimum condition (Table 1).

Table 1. Optimization of DODH reaction in small scale



12 14

entry	Catalyst (eq.)	reductant / solvent	temp. (°C)	time (h)	result
1	$MeReO_3$(0.05 eq.)	Na_2SO_3 / THF	120*	17	no rxn
2	$MeReO_3$(0.05 eq.)	isopropanol	120*	12	no rxn
3	$MeReO_3$(0.05 eq.)	cyclohexanol	120	12	11%
4	$MeReO_3$(0.05 eq.)	1-heptanol	200*	12	84%
5	$MeReO_3$(0.05 eq.)	3-pentanol	150*	12	53%
6	$MeReO_3$(0.05 eq.)	1-butanol	150*	12	72%
7	$MeReO_3$(0.05 eq.)	1-butanol	reflux	12	96%
8	Re_2O_7(0.01 eq.)	1-butanol	reflux	12	50%
9	Re_2O_7(0.02 eq.)	1-butanol	reflux	12	93%
10	Re_2O_7(0.05 eq.)	1-butanol	reflux	12	>99%
11	MoO_3	1-butanol	reflux	12	trace
12	WO_3	1-butanol	reflux	12	trace

* the reaction was conducted in pressure tube

Concerning reducing agent, heterogeneous sulfite was initially applied where THF was used as a solvent, but desired muconate was not obtained at all (entry 1). According to the result of entry 1, solubility of the substrate in the given solvent and homogeneity of reducing agent were highly relevant to reaction efficiency. Therefore, we secondly applied various alcohols intended to act as both reducing agent and solvent, which dissolve the substrate well and was mixed with other reagents. When isopropanol was used, desired product was not obtained at all, that might due to the low boiling point. However, cyclohexanol gave only small amount of the product in spite of its high boiling point. Cyclic alcohol seemed not to be suitable as a reducing agent. (entry 2 and 3). On the other hand, dialkyl muconate was successfully obtained in good yield with 1-butanol, 3-pentanol and 1-heptanol which are aliphatic primary or secondary alcohol having high boiling point (entry 4-7). Among those three alcohols, 1-butanol is most suitable for our process because of its appropriate boiling point for both reaction and work-up process compared to 1-heptanol having excessively high boiling point that is hard to remove after the reaction. It is cheaper and better in supply compared to 3-pentanol. Moreover, it is one of the well-known green solvents that is meaningful in environmental point of view.[23] Regarding catalyst, rhenium based catalyst showed the superior activity than

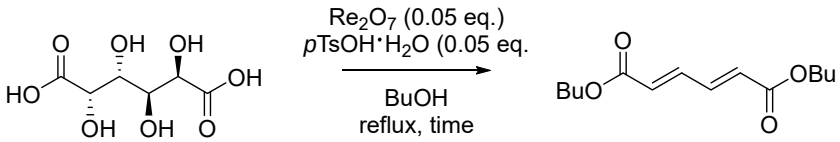
other element-based catalyst such as W or M_o (entry 11-12). The formation of catalyst was not highly effect on the result (entry 7 and 10), whereas the amount of catalyst affected the reaction result. At least, 2 equivalent of rhenium catalyst seemed to be needed to afford the muconate in good yield (entry 8-10). Consequently, the optimum condition of DODH reaction was established that was proceeded under mild reflux condition with the use of oxo-rhenium catalyst ($MeReO_3$ or Re_2O_7) and 1-butanol (entry 7 and 10).

1.2.3 Large-scale DODH reaction

Under the optimized reaction condition, reaction scale was intensively extended (Table 2). In small scale from 210 mg to 1 g, general DODH reaction time of 12 h was enough for the excellent yield (entry 1-2). However, when the reaction scale was increased to 5 g, the conversion sharply deceased to 18% yield (entry 3). We hypothesized that the result was due to the deactivation of rhenium catalyst, i.e. poisoning, fouling, and ageing, which could be caused by following reasons: in situ generated water during the reaction and inherent or flowed-in air possessing oxygen. Even though generated water was removed by dean-stark trap as soon as possible, some of water possibly remained in short time before it vaporized and may affect catalyst activity. Therefore, the starting material was changed to dibutyl galactarate instead of galactaric acid to reduce catalyst deactivation during the esterification. Because the most of starting material was recovered as its dibutyl ester form when the reaction conversion was low, which implied catalyst activity decreased in the stage of esterification. This assumption was additionally supported by the result that dibuty muconate was obtained with only rhenium catalyst without the help of additional acid catalyst, which means rhenium catalyst involved in the esterification like Lewis acid. That is the reason that esterification was preceded before DODH

reaction in the presence of solely Brønsted-Lowry acid catalyst. Besides, better solubility of resulting dibutyl galactarate might increases DODH reaction efficiency. As a result, dibutyl galactarate was converted to muconate in slight increased yield of 45% (entry 4).

Table 2. Large scale DODH reaction



12 **14a**

No.	scale	1-butanol (ml)	time (h)		result (%)
			pre-esterification	DODH reaction	
1	210 mg (1 mmol)	30	-	12	>99
2	1 g (5 mmol)	80	-	12	>99
3	5 g (24 mmol)	400	-	12	18%
4	5 g (24 mmol)	400	ester*	12	45%
5	5 g (24 mmol)	400	6	24	51%
6	5 g (24 mmol)	400	6	24**	>99
7	5 g (24 mmol)	100	6	24	>99%

* dibutyl galactarate was used as a starting material

** catalyst was added twice per 0.25 equivalents each

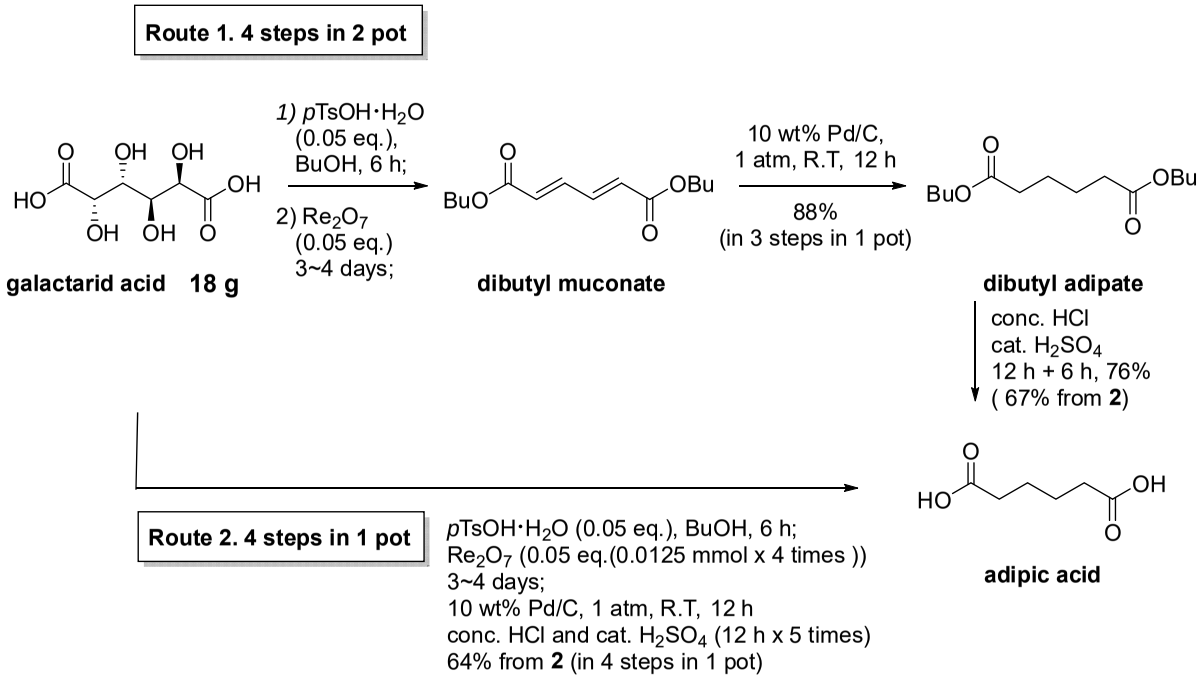
However, because the additional esterification step could be problematic in large scale reaction, we conducted *in situ* esterification in the presence of *p*-toluenesulfonic acid which is also used for DODH reaction with rhenium catalyst. In the concept of pre-esterification, *in situ* generated dibutyl galactarate immediately underwent DODH reaction by adding rhenium catalyst after esterification. At first, the reaction mixture was cloudy due to the poor solubility of galactaric acid in 1-butanol, and it turned to be clear when esterification is completed. At this point, the rhenium catalyst was added for following DODH reaction. This reaction system was organized to allow rhenium to act specifically as DODH catalyst. Overall reaction including esterification and DODH reaction were conducted using reflux condenser equipped with dean-stark trap to prevent exposure of catalyst from *in situ* generated water during the reaction. Additionally, to reduce the effect of oxygen on catalyst deactivation, 1-butanol solvent was firstly degassed by Ar bubbling to remove inherent oxygen contents before the reaction, and the reaction was proceeded under Ar atmosphere to prevent inflow air. As a result, the yield slightly increased to 51% (entry 5). Under the same reaction condition of entry 5, sometimes moderate to good yield was obtained when the reaction time was prolonged more than 24 h until full conversion, which was checked by ^{1}H NMR of aliquot sample. But, it was

hard to control because it barely and irregularly occurred, which is a critical problem in industrial process. Perhaps, that is because catalyst deactivating factors were not completely prevented. In consequence, we changed the way of catalyst addition to portion-wise compensating catalyst deactivation. It was intended to constantly maintain activity over the whole reaction time by regularly feeding fresh new catalyst. The total amount of catalyst was not changed, desirably 0.05 equivalents, but the only difference was number of catalyst addition added twice per 0.025 equivalent. This resulted in surprisingly increased overall yield of >99%. Fortunately, it was reproducible even with reduced amount of 1-butanol to quarter, nevertheless excess amount of alcohol effected on the result even in small scale (entry 6). From this result, the crucial factors of DODH reaction for large scale were demonstrated that is esterification, removal inherent and inflow oxygen gas, prolonged reaction time, and portion-wise addition of catalyst, all of which are related to catalyst activity.

1.2.4 One-pot process for adipic acid

With optimized large-scale DODH reaction, we synthesized adipic acid from galactaric acid with our concise one-pot synthetic process (Scheme 17). To avoid complex synthetic process, we did not isolate dibutyl muconate or dibutyl adipate. Without any other purification, obtained crude muconate was exposed to mild catalytic hydrogenation condition of room temperature and normal pressure of hydrogen gas affording dibutyl adipate. This reaction sequence was designed to increase low hydrogenation efficiency arising from the poor solubility of muconic acid in general organic solvent. After removing volatile components under reduced pressure, crude dibutyl adipate was exposed to acidic hydrolysis condition producing desired adipic acid in overall yield of 64% in one-pot as a white needle like solid after recrystallization with acetonitrile. As aforementioned, because dibutyl adipate could be used in itself (Cetiol®B, BASF trade name), we also tried isolating dibutyl adipate by vacuum distillation, which is more suitable for large scale than column purification, in high purity at yield of 88% as colorless liquid. And it could be further transformed to adipic acid after acidic hydrolysis. Practically, adipic acid was obtained from dibutyl adipate **15** in 76% yield over 2 steps. Although hydrolysis efficiency was somewhat better in stepwise reaction, the overall yield was similar with the previous

result of one-pot procedure. In conclusion, galactaric acid was efficiently converted to the adipic acid **16** in large scale of 18 g through 4 step reaction of esterification, DODH reaction, hydrogenation and acidic hydrolysis in one-pot with good yield.



Scheme 17. One-pot synthesis of adipic acid from galactaric acid

1.3 Exprimental Details

General remarks. Unless otherwise noted, materials were obtained from commercial supplier and were used without further purification. Galactaric acid (**12**), Re_2O_7 and palladium 10% on carbon were purchased from Alfa aeasar Co. Ltd., and $MeReO_3$, glucaric acid mono-potassium salt (**10**) was purchased from Sigma aldrich Co. Analytical thin layer chromatography (TLC) was performed by using Merck 60 F254 glass plates pre-coated with a 0.25 mm thickness of silica gel and monitored under UV light (254 nm). The crude products were column chromatographed on Merck Kieselgel 60 (70-230 mesh) silica gel using solvent mixtures of hexane and ethyl acetate as eluents. Melting points were determined with an open capillary melting point apparatus (Electrothermal IA9100). NMR spectra were measured on a Bruker AVIII400 instrument as solutions with TMS as an internal standard (^1H at 400 MHz and ^{13}C at 100 MHz) unless otherwise stated and data were reported as follows in ppm (δ) from TMS: chemical shift (multiplicity, coupling constant in Hz, integration). The percentage yields of each product were calculated by dividing the amount of the desired product obtained after purification by the theoretical yields.

General procedure for DODH reaction To a solution of galactaric acid (210 g, 1 mmol) in 1-butanol (30 ml) was added Re_2O_7 (24 mg, 0.05 mmol) or $MeReO_3$ (12 mg, 0.05 mmol) and *p*TsOH·H_2O (10 mg, 0.05 mmol) at room temperature. The resulting mixture was stirred vigorously at reflux condition for 12 h with dean-stark strap. After completion of reaction, the mixture was cooled to room temperature then the volatile components were removed under reduced pressure. The dark brown syrup mixture were purified by column chromatography on silica gel (hexane/EtOAc =16:1) afforded desired *trans,trans*-dibutyl muconate as colorless needle like crystal; mp 39~40 °C (lit.[24a] 34~35 °C); ^{1}H NMR ($CDCl_3$) δ 7.32-7.28 (m, 2H), 6.21-6.17 (m, 2H), 4.18 (t, J = 6.6 Hz, 4H), 1.68-1.64 (m, 4H), 1.43-1.38 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 166.0, 140.7, 128.4, 64.7, 30.6, 19.1, 13.67; Anal. calcd for $C_{12}H_{22}O4$: C, 66.12 H, 8.72; Found: C, 66.51 H, 8.78

One-pot procedure for adipic acid To a solution of galactaric acid (18.0 g, 85.6 mmol) in Ar bubbled 1-butanol (360 ml) was added *p*TsOH·H_2O (814 mg, 4.28 mmol) at room temperature under Ar atmosphere. The resulting mixture was stirred vigorously at reflux condition until the mixture to be clear with dean-stark strap. After reaction completed, the mixture was cooled to room temperature then Re_2O_7 (345 mg, 0.71 mmol)

was added to the mixture. The resulting mixture was refluxed again for 84 h, and during the reaction, the other 5 portions of Re_2O_7 (345 mg, 0.71 mmol x 6 times) were regularly added. After the reaction, the volatile components were removed under reduced pressure. The resulting dark brown syrup mixture was diluted with EtOAc (300 ml) then 10 wt% palladium on carbon (1.20 g, 1.13 mmol) was added. The reaction mixture was stirred for 3 days at room temperature under 1 atm of hydrogen atmosphere. After the reaction, the mixture was filtered through a celite pad with excess ethyl acetate, then the filtrate was concentrated. The obtained mixture was hydrolyzed with concentrated hydrogen chloric acid (100 ml) and catalytic sulfuric acid (0.3 ml) under reflux condition for 12 h. The resulting biphasic mixture were separated, then upper side oily layer refluxed again with concentrated hydrogen chloric acid (50 ml) and sulfuric acid (0.5 ml) for another 6 h under reflux condition and bottom side aqueous mixture was concentrated *in vacuo* to afford crude adipic acid. After second hydrolysis, combined crude adipic acid was purified by recrystallization in acetonitrile to give adipic acid **1** (8.01 g, 54.8 mmol, 64%) a white needle crystal; mp 152~153 ºC (lit.[24b] 152~153 ºC); ^{1}H NMR (DMSO-d_6) δ 2.21 (m, 4H), 1.50 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 174.8, 33.8, 24.5; Anal. calcd for $C_6H_{12}O_4$: C, 49.31 H, 6.90; Found: C, 49.41 H, 7.13.

2. Recyclable green process for bio-based adipic acid using ionic liquid

2.1 Introduction

2.1.1 Rhenium catalyst recycling

DODH reaction is one of the most promising C-O bond cleavage method, however, it still has some challenges to apply industry. Most of all, relatively rare and expensive oxo-rhenium catalyst is considered as a major drawback. Above mentioned, to overcome this challenge, various metal catalysts have been applied to develop more abundant and cheaper alternatives. However, rhenium based catalysts generally show superior reactivity than those of other metal catalyst regardless of substrate or reducing agent. Therefore, the focus of recent research has been moved on recycling of rhenium catalyst using immobilized heterogeneous catalysts.[25] Some of result have been reported, it still have some problems on the low efficiency or additional catalyst preparation. Regarding this, one impressive result was obtained by Zhang *et al*. using polymer-supported rhenium catalysts.[25c] However, it still required to further research improving the recycling efficiency, which encouraged us to develop another recyclable DODH reaction.

2.1.2 Ionic liquids

In last decade, ionic liquid, a salt completely composed of cations and anions in the liquid state, has attracted much interest with diversified rage of application. The research on ionic liquid have recently been extended and intensified in green chemistry due to its reusability as well as the feature showing no detectable vapor pressure. In same context, ionic liquid has been applied for recyclable catalysis, it shows high efficiency and selectivity compared to heterogeneous catalysis due to its homogeneity.[26] To be specific, it has been introduced as a green reaction media in biphasic catalysis[26d-k] along with immobilized metal-containing ionic liquid catalysis.[26k-0]

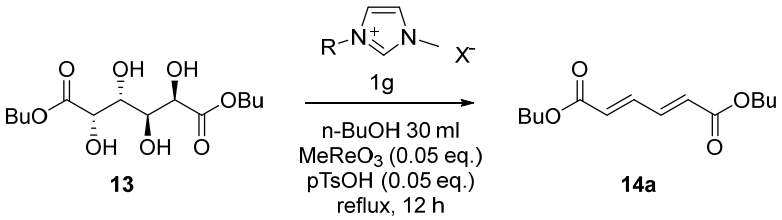
Motivated by recent results, we have introduced ionic liquid as a reaction media for DODH reaction in order to easy separation and recycling. Especially, when it was separated from the reaction mixture it was dissolving the used rhenium catalyst, and recycled without significant loss of activity. Therefore, the most important property of ionic liquids is its unusual solubility dissolving a specific range of organic solvent. Ionic liquid normally exhibits similar polarity with methanol or acetonitrile. But, unlike these kinds of solvents, it is immiscible with non-polar organic solvents like diethyl ether and hexane. Furthermore, its solubility could be more precisely adjusted by its structure modification.[26]

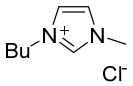
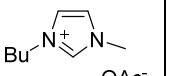
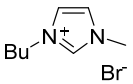
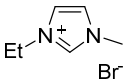
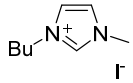
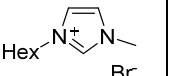
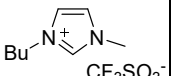
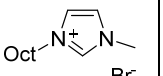
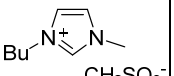
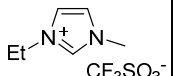
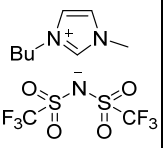
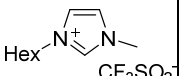
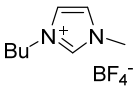
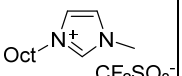
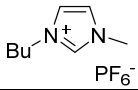
2.2 Result and discussion

2.2.1 DODH reaction with various ionic liquid

In order to use ionic liquid as a reaction media, it is required to be chemically and thermally stable to avoid interruption on the reaction. In this aspect, various ionic liquids were screened under previously optimized reaction condition described above. At first, the reaction started from galactaric acid. However, the conversion was significantly low because of the low solubility of galactaric acid in the mixture of ionic liquids and 1-butanol. Therefore, starting material was altered to its dibutyl ester form to increase solubility. To investigate the effect of ionic liquid, we firstly applied imidazolium-based ionic liquids, one of the well-known ionic liquids (Table 3). Above mentioned, the properties of ionic liquid could be controlled by structural modification. In order to find appropriate ionic liquid, imidazolium-based ionic liquid was diversified on both cation and anion.[27] First, the anion effect of ionic liquids was examined in the conversion of galactarate to muconate (entry 1-9). Negligible conversion was observed with 1-butyl-3-methyl imidazolium halide, BF_4 (tetrafluoroborate), and PF_6 (hexafluorophosphate) (entry 1-3, 7, 8). In the case of acetate anion, desired product was not obtained at all (entry 9). Although the solubility of these

Table 3. DODH reaction with various imidazolium-based ionic liquids



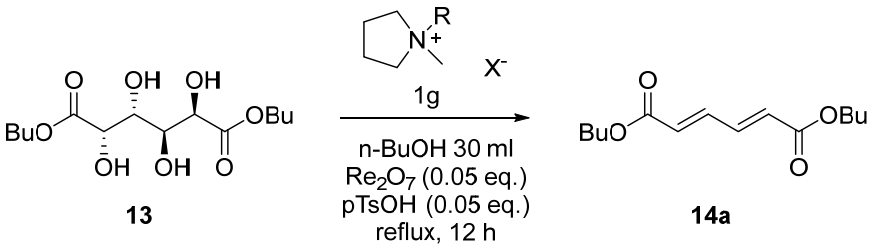
No.	IL		result	No.	IL		result
	Abbre.	structure	(%)		Abbre.	structure	(%)
1	[C_4MIm]Cl		20	9	[C_4MIm][OAc]		-
2	[C_4MIm]Br		33	10	[C_2MIm]Br		-
3	[C_4MIm]I		16	11	[C_6Mim]Br		19
4	[C_4MIm][TfO]		>98*	12	[C_8Mim]Br		10
5	[C_4MIm][mesy]		47*	13	[C_2MIm][TfO]		78
6	[C_4MIm][TFSI]		93	14	[C_6MIm][TfO]		80
7	[C_4MIm][BF_4]		5	15	[C_8MIm][TfO]		68
8	[C_4MIm][PF_6]		16	*Re_2O_7 was used as metal catalyst instead of $MeReO_3$			

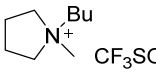
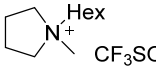
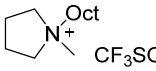
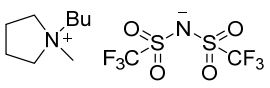
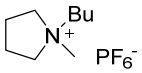
ionic liquids seem suitable to give homogenous mixture, those of anions may have negative effect on DODH reaction. Whereas, triflate and TFSI anion afforded the muconate in almost quantitative yield (entry 4, 6). Interestingly, mesylate anion showed relatively low yield, even though it has similar structure with triflate (entry 5). Second, the cation effect was demonstrated according to the length of alkyl substituent on cation. The alkyl chains at C1 position were varied in ethyl, butyl, hexyl, and octyl. Although butyl group showed slightly better result than others, no significant effect was observed with the same anion. (entry 5 and 13-15)

Based on the result, it is expected that the anion is more closely related to the DODH reaction. For further investigation on the effect of cation to DODH reaction, Pyrrolidinium-based ionic liquids were additionally examined with three different anions: triflate, TFSI and PF_6. As expected, regardless of cation, both triflate and TFSI anions showed good performance and PF_6 produced only trace amount of dibutyl muconate (entry 17-19).

Consequently, [C_4MIm][TfO], [C_4MIm][TFSI], and [C_4MIm][TfO] is appropriate ionic liquid, these results indicate that triflate or TFSI anion play a pivotal role when it is used as DODH reaction media.

Table 4. DODH reaction with various Pyrrolidinium-based ionic liquids



No.	IL		result (%)
	Abbre.	structure	
1	[C_4MPyrr][TfO]		>98
2	[C_6MPyrr][TfO]		>98
3	[C_8MPyrr][TfO]		>98
4	[C_4Mpyrr][TFSI]		>98
5	[C_4MPyrr]PF_6		trace

2.2.2 Recycling of rhenium catalyst using ionic liquid

Our strategy for rhenium catalyst recycling is described in Figure 9. Appropriate solubility is most important feature to use ionic liquid for DODH reaction as recyclable reaction media. The Ionic liquid should be miscible with the reagents and solvent during the reaction. After the reaction, immiscible ionic liquid layer was separated form organic solvent which is added for dissolving the product. When the ionic liquid is separated from organic solvents, it has to contain both rhenium and acid catalyst with enough activity to be reused several times. After separation, simply adding starting material and butanol, desired muconate was produced again under flux condition.

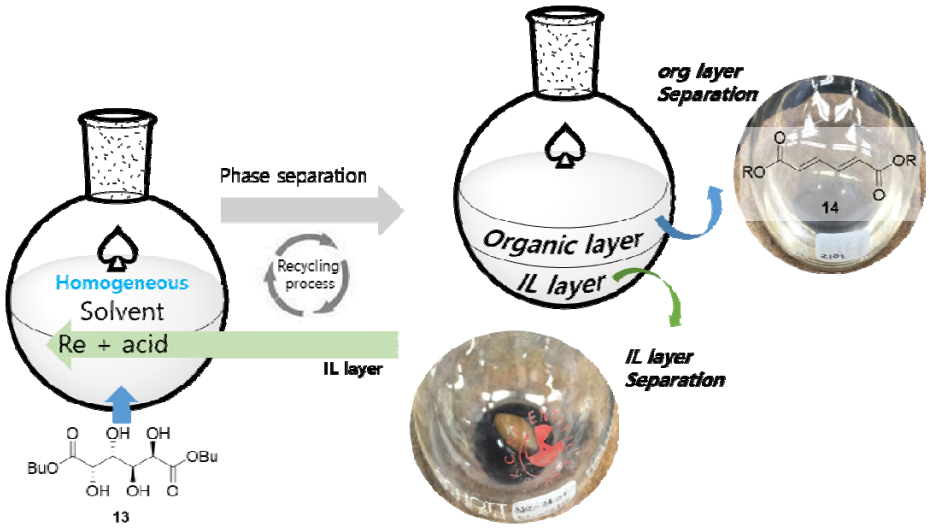


Figure 9. Recycling process diagram of DODH reaction

Based on the result of the screening study toward various ionic liquids, the intensive study has been accomplished to find optimum condition for recycling of liquid-mediated DODH reaction. Among various ionic liquid, the reusability was examined with triflate and TFSI anions which showed good DODH efficiency. In case of TFSI, the yield, the yield was excellent but the yield was rapidly decreased as repeating ionic liquid recycling (Fiqure 10).

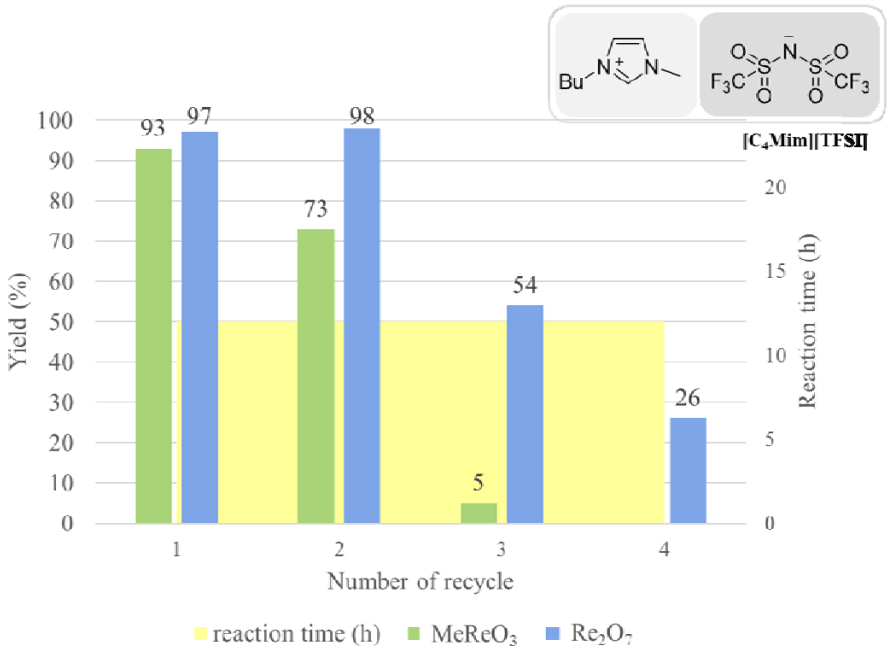


Figure 10. Catalyst reusability test with [C4MIm][TFSI]

Supposedly, low viscosity value derived from TFSI anion caused the loss of ionic liquid during decantation. On the other hand, [C_4MIm][TfO] showed much better recyclability until 5th cycle (Figure 11). The high viscosity value of trifilate anion might increase the separation efficiency. As a further investigation on viscosity effect, long alkyl chain substituent was introduced to imidaziolium cation, because it is known to increase the viscosity of ionic liquid. However, the long alkyl chain rather disturbed separation of ionic liquid by increasing organic solubility. The ionic liquid was even detected in organic layer after evaporation, which also means loss of the catalyst. With

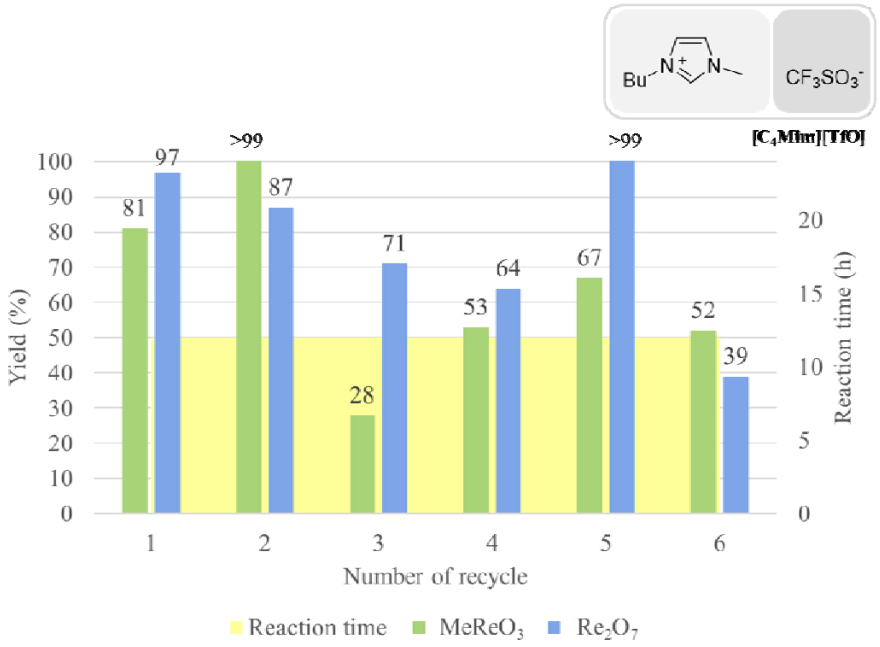


Figure 11. Catalyst reusability test in [C_4MIm][TfO]

similar reason, pyrrolidium-based ionic liquid was also inefficient. Even though pyrrolidium-based ionic liquid generally shows high viscosity, it also enhanced organic solubility at the same time resulted in low recyclability caused by loss of ionic liquid.[28] As a result, it was proven that [C_4MIm][TfO] was most appropriate for the recyclable DODH reaction media.

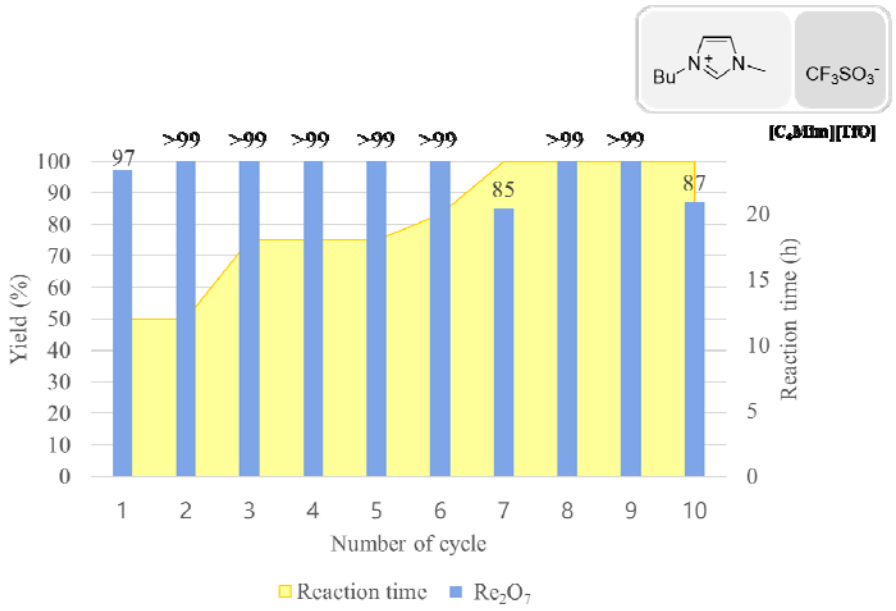


Figure 12. Optimized Re_2O_7 catalyst recycling in [C_4MIm][TfO]; prolonged reaction time

However, even with [C_4MIm][TfO], the conversion was declined from 3rd cycle, which might be caused by catalyst deactivation or leaching (Figure 12). Therefore, reaction time was prolonged to compensate decreased reactivity of catalyst. Fortunately, catalyst deactivation was insignificant to

be covered enough by controlling the reaction time as shown in Figure 12. Consequently, the ionic liquid was reused up to 10th cycle to produce desired product in excellent yield by gradually increasing the reaction time from 12 h to 24 h. In addition, the muconate **14a** was almost quantitatively obtained until 5th cycle by replenishing 0.5~1 mol% of fresh catalyst in equally 12 h (Figure 13).

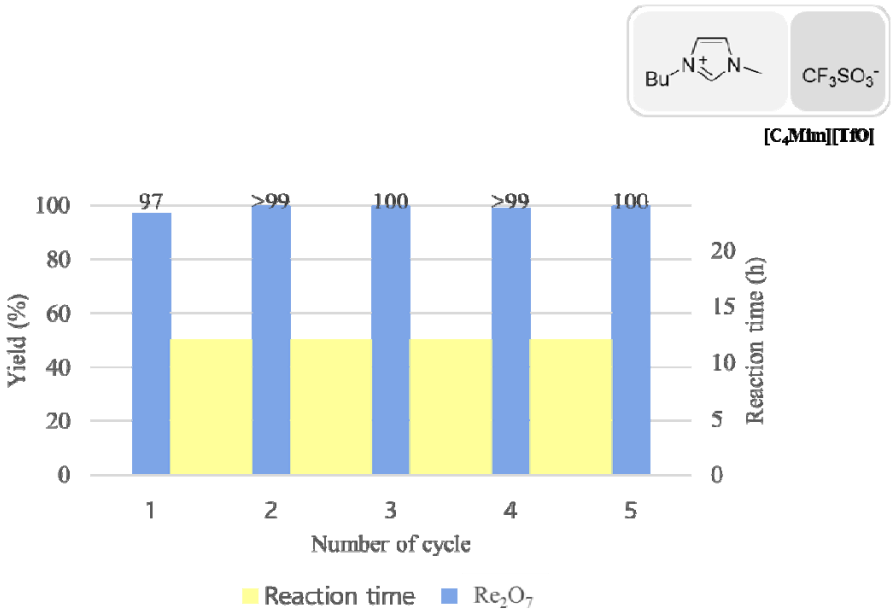


Figure 13. Optimized Re_2O_7 catalyst recycling in [C_4MIm][TfO]; catalyst replenishment

In order to precisely analyze the catalyst deactivation from the ionic liquid, we performed ICP-Ms to measure the amount of rhenium dissolved in ionic liquid. Catalyst leaching was detected until 5^{th} cycle, on the other hand, there was no significant difference after 5^{th} cycle until 10^{th} cycle. We also carried out reusability test with 0.003 equivalent of rhenium catalyst for 24 h from the 1^{st} cycle, because the leaching could be related to the saturated concentration of catalyst in ionic liquid. However, it was not quite efficient even under prolonged reaction. In the same context, the amount of ionic liquid was also varied form 500 mg to 4 g, but it did not seem to affect the result.

2.3 Experimental Details

General remarks Unless otherwise noted, materials were obtained from commercial supplier and were used without further purification. Galactaric acid (**12**), salt and Re_2O_7 were purchased from Alfa Aeasar Co. Ltd., and $MeReO_3$ and $[C_4MIm][TfO]$ were purchased from Sigma aldrich Co. Another ionic liquid, $[C_nMIm][X]$[29] and $[C_nMPyrr][X]$[29g,29h,30], were prepared by modified known procedure. Analytical thin layer chromatography (TLC) was performed by using Merck 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel and monitored under UV light (254 nm). The crude products were column chromatographed on Merck Kieselgel 60 (70-230 mesh) silica gel using solvent mixtures of hexane and ethyl acetate as eluents. Melting points were determined with an open capillary melting point apparatus (Electrothermal IA9100). Low and high resolution mass spectra were measured by the EI or FAB ionization method (JEOL, JMS-600W, JMS-700, 6890 Series). Rhenium contents in ionic liquids were determined by Varian 820-MS. NMR spectra were measured on a Bruker AVIII400 instrument as solutions with TMS as an internal standard (^1H at 400 MHz and ^{13}C at 100 MHz) unless otherwise stated and data were reported as follows in ppm (δ) from TMS: chemical shift

(multiplicity, coupling constant in Hz, integration). The percentage yields of each product were calculated by dividing the amount of the desired product obtained after purification by the theoretical yields.

General procedure for DODH reaction with ionic liquids To a solution of dibutyl galactarate **13** (0.161 g, 0.5 mmol) in mixed solution of IL (1 g) and 1-butanol (30 ml) was added Re_2O_7(14 mg, 0.03 mmol) or $MeReO_3$ (7 mg, 0.03 mmol) and *p*TsOH·H_2O (6 mg, 0.03 mmol) at room temperature. The resulting mixture was stirred vigorously at reflux condition for 12 h with dean-stark strap. After completion of reaction, the mixture was cooled to room temperature then the volatile components were removed under reduced pressure. The dark brown syrup mixture was diluted with diethyl ether (3 x 30 ml) and stirred for additional 30 min. The diethyl ether layers were decanted and combined organic layers were concentrated *in vacuo*, resulting dark brown liquid. Purification by column chromatography on silica gel (hexane/EtOAc=16:1) afforded desired *trans,trans*-dibutyl muconate **14a** as a colorless needle like crystal.

The remained IL was recycled after removing the volatiles under reduced pressure. The IL including Re_2O_7 and pTsOH·H_2O were ready to use again only after vacuum drying. By simply adding dibutyl

galactarate and 1-butanol, above procedure were repeated in another 9 times.

Conclusion

A green and sustainable process for adipic acid from C6 sugar derived galactaric acid has been developed. For the first, facile and efficient one-pot process which is appropriate for industrial process has been developed. Practically, 18 g of galactaric acid derived from galactose was successfully converted to adipic acid. The two pairs of hydroxyl group on galactaric acid were efficiently removed by rhenium-catalyzed DODH reaction. While the full conversion of DODH reaction was challengable in large scale, it has been improved by minimize catalyst deactivation through pre-esterification and portion-wise addition under Ar atmosphere. After recrystallization with MeCN which is only and first purification, desired adipic acid was obtained as a white solid in 64% yield. Second, in order to enhance the cost efficiency of DODH reaction, ionic liquid was introduced to recycle relatively rare and expensive rhenium catalyst. Various ionic liquid was applied to the reaction, among those, [BMIm][OTf] showed superior result in terms of reaction efficiency and reusability. Dissolving in [BMIm][OTf], rhenium catalyst reused up to 10 times to removed oxygen contents present in dibutyl galactarate affording a key intermediate of adipic acid. As increasing

the number of running cycle, the used catalyst seemed to be deactivated, but it was not so significant to be covered by prolonged reaction time. However, there is still some room for improvement in terms of catalyst recycling optimization.

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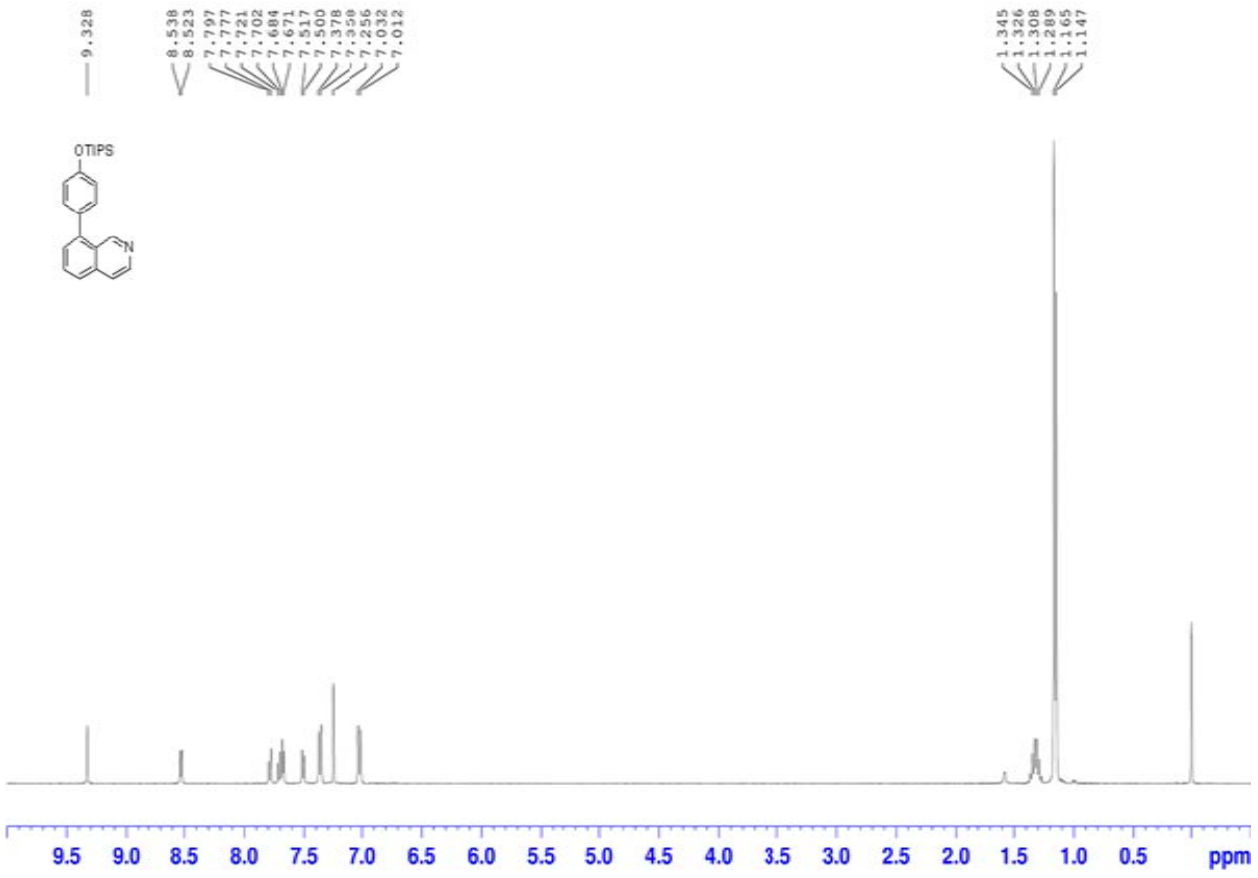
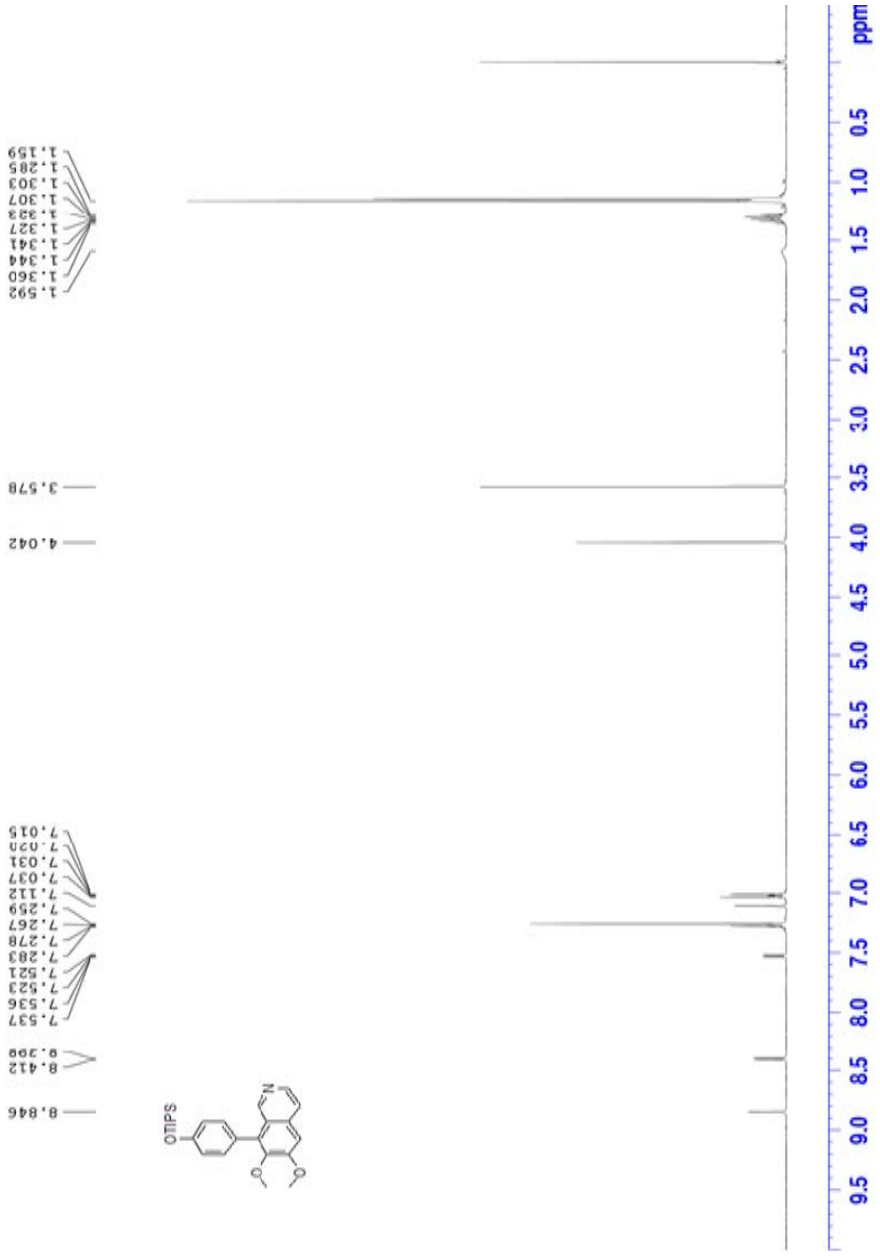
Appendices

List of ^{1}H-NMR Spectra of Selected Compounds

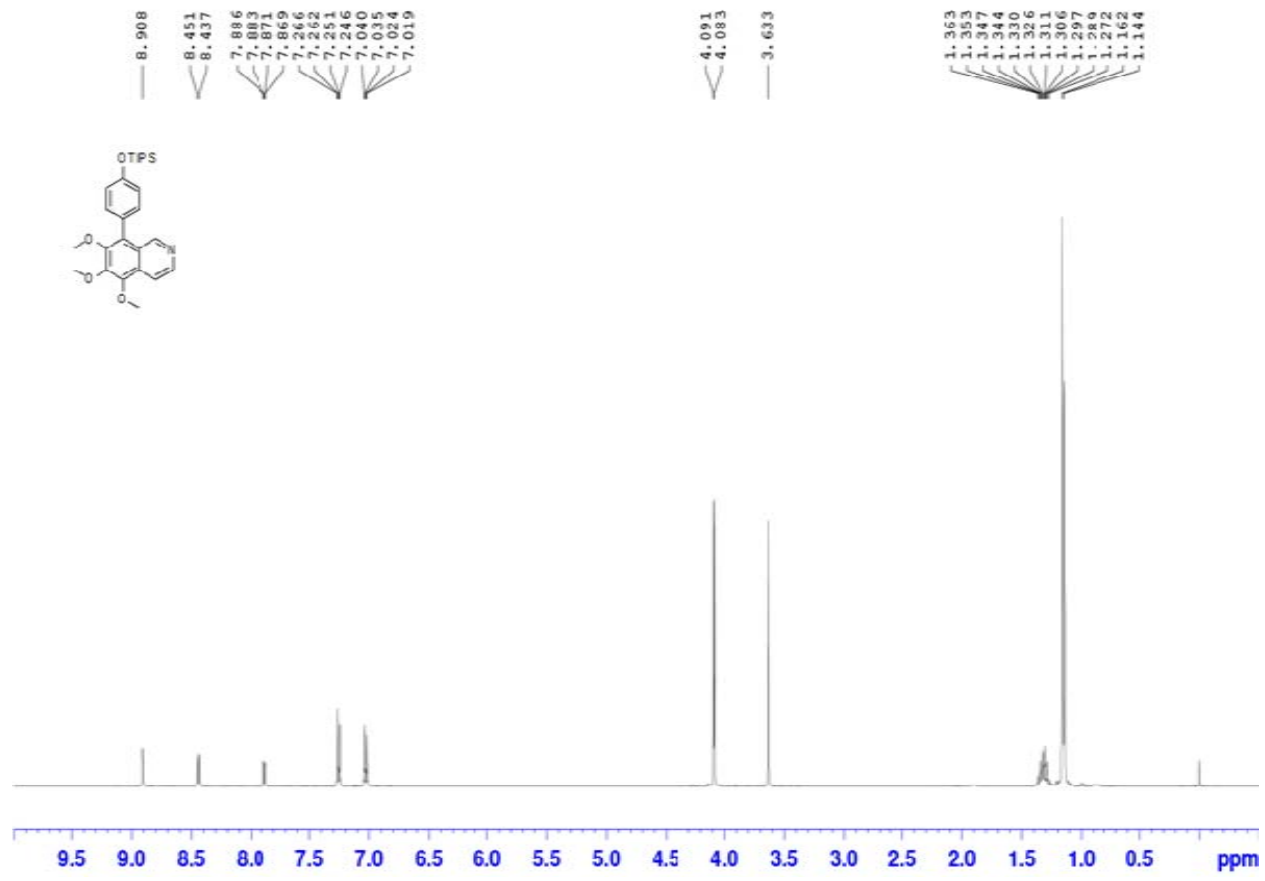


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **4a**

400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **4b**

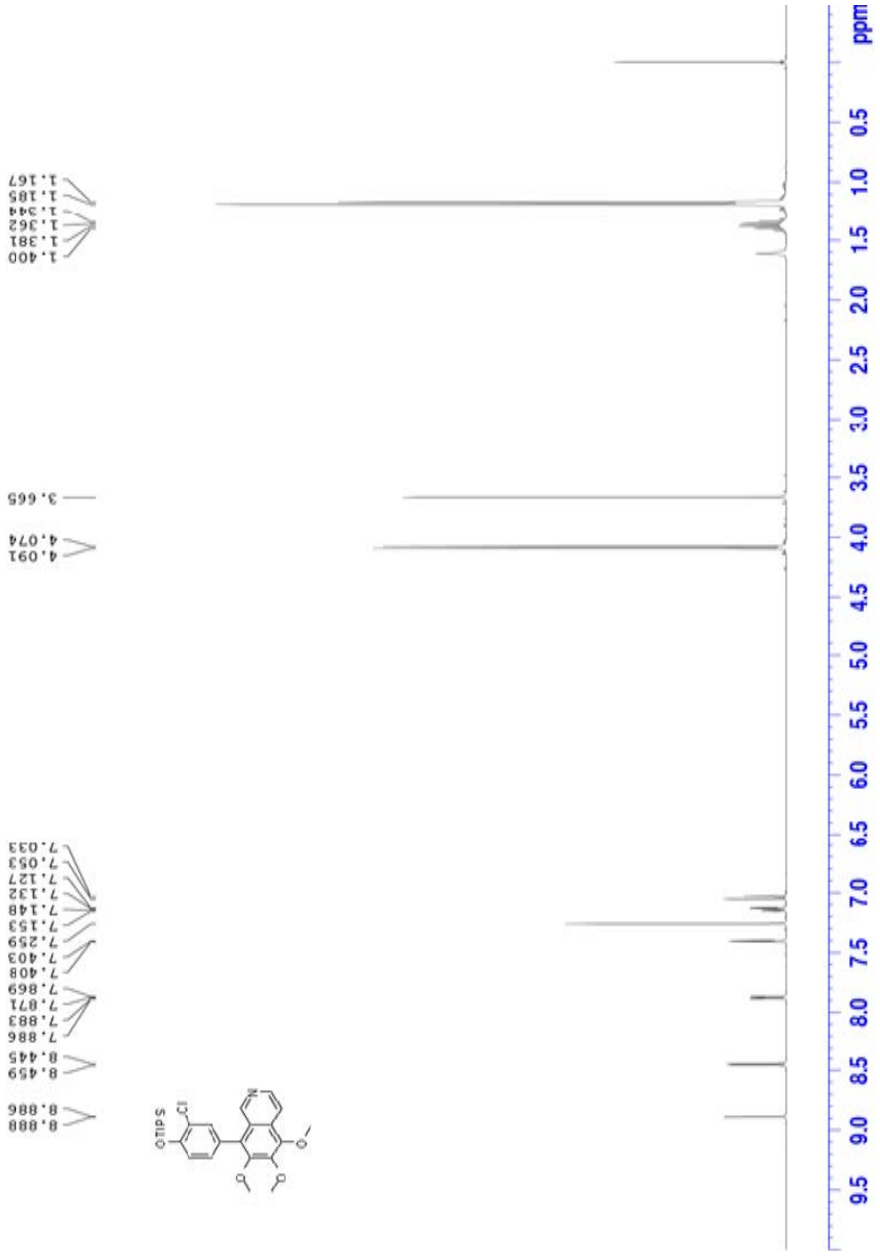


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **4c**

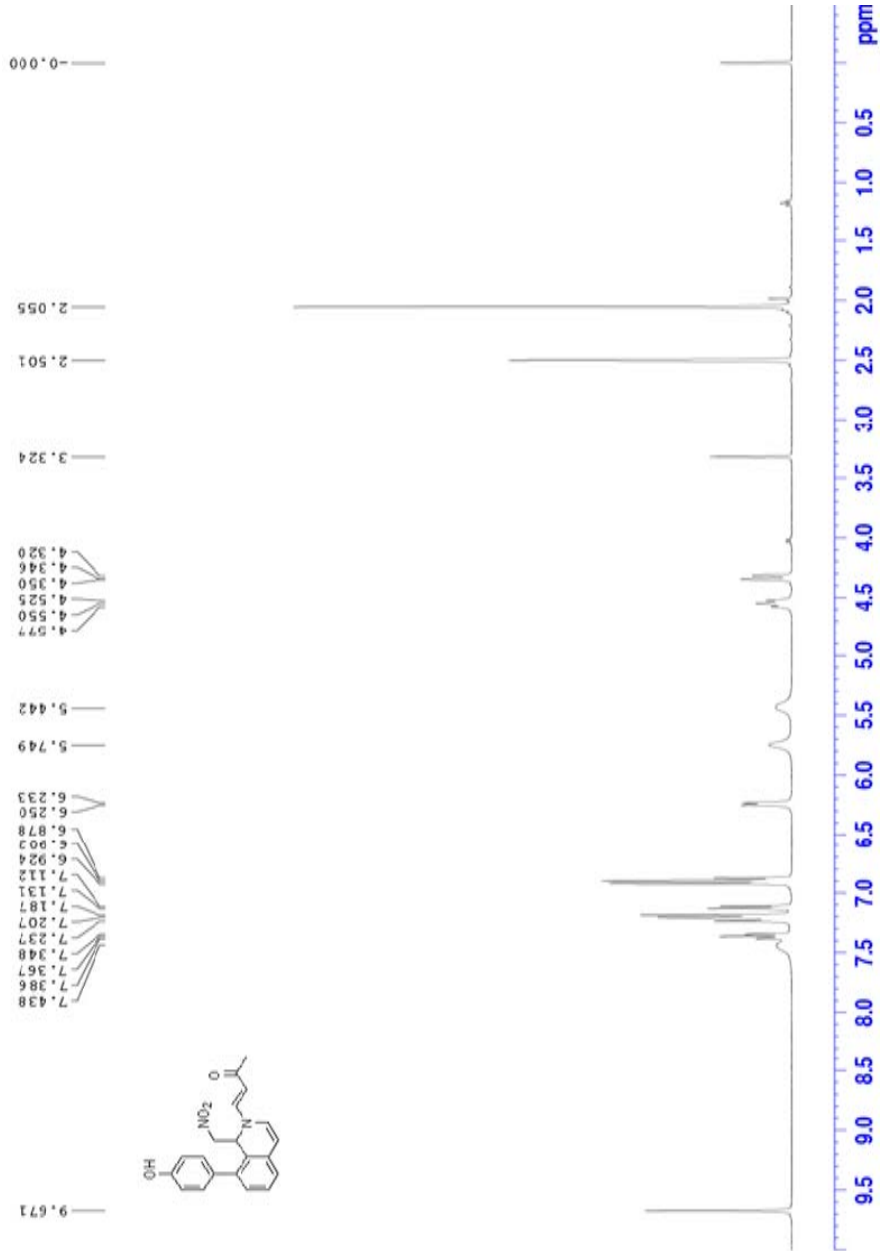


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **18**

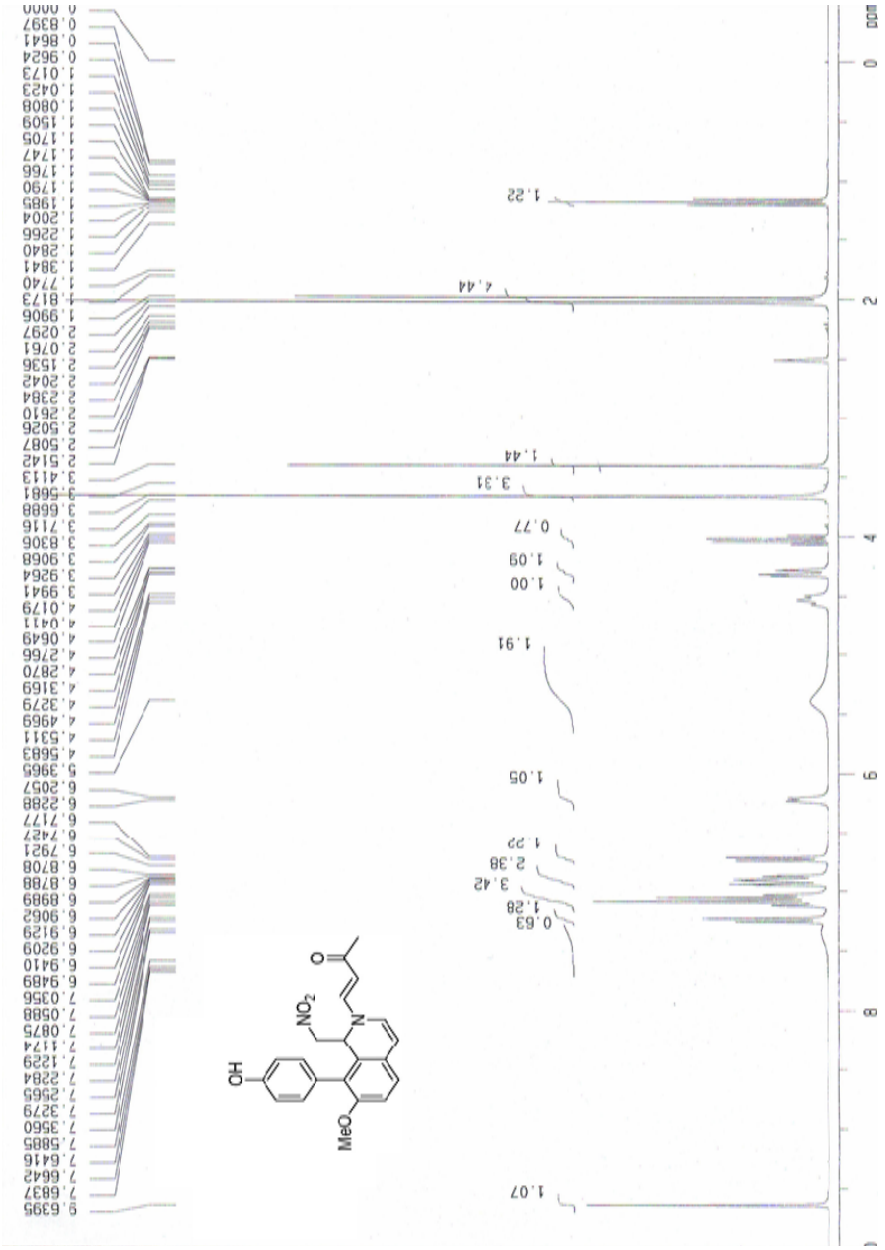
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **7c**



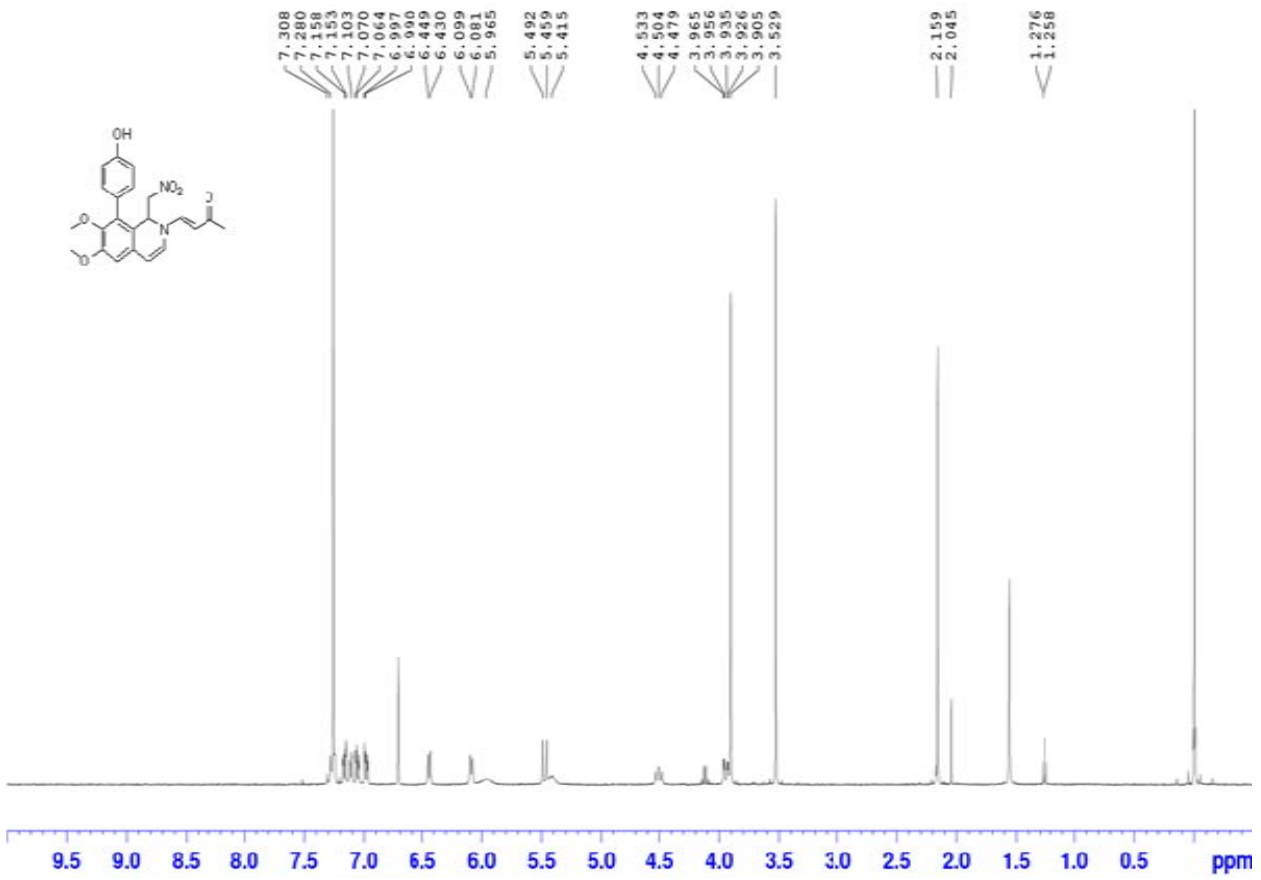
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **7d**



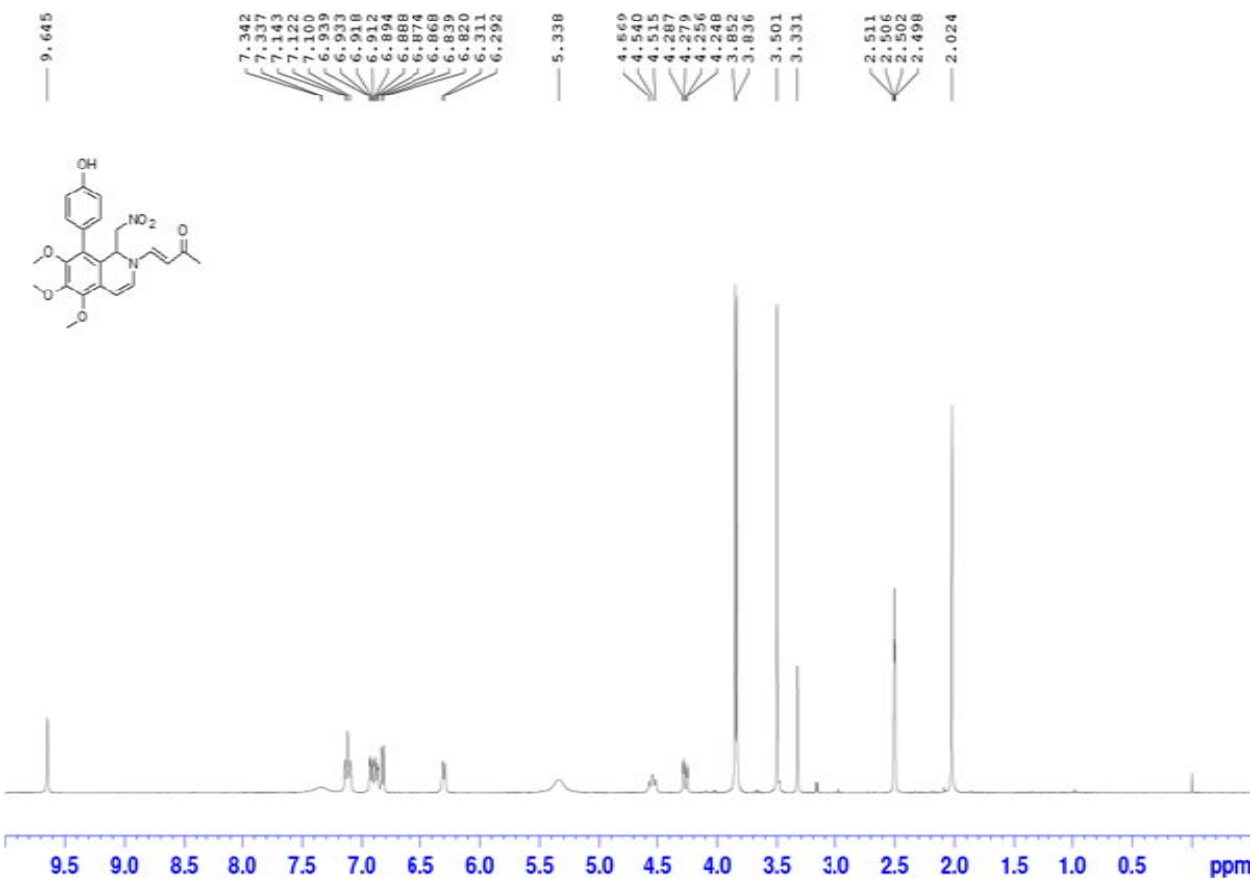
400 MHz ^{1}H-NMR spectrum (DMSO-d_6) of compound **6a**



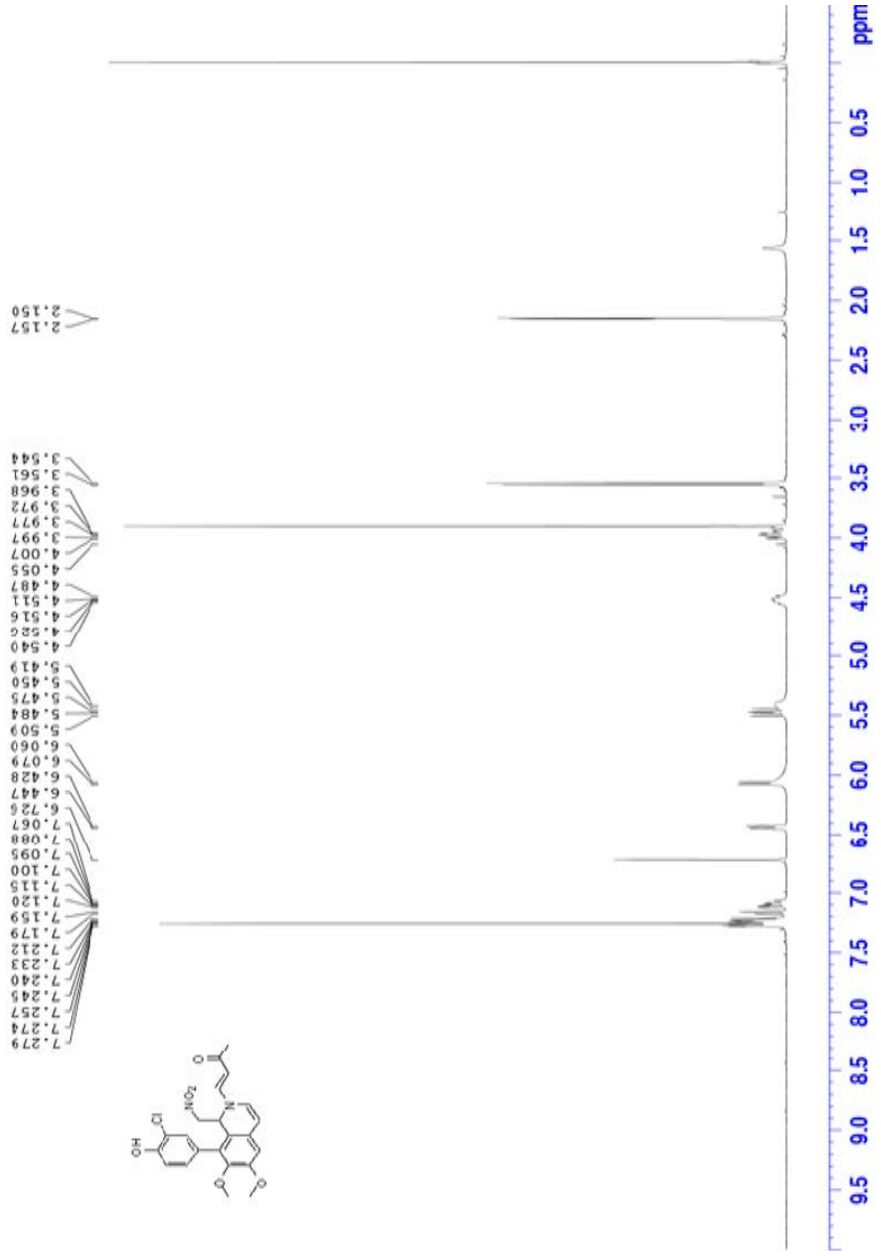
300 MHz ^{1}H-NMR spectrum (DMSO-d_6) of compound **6b**



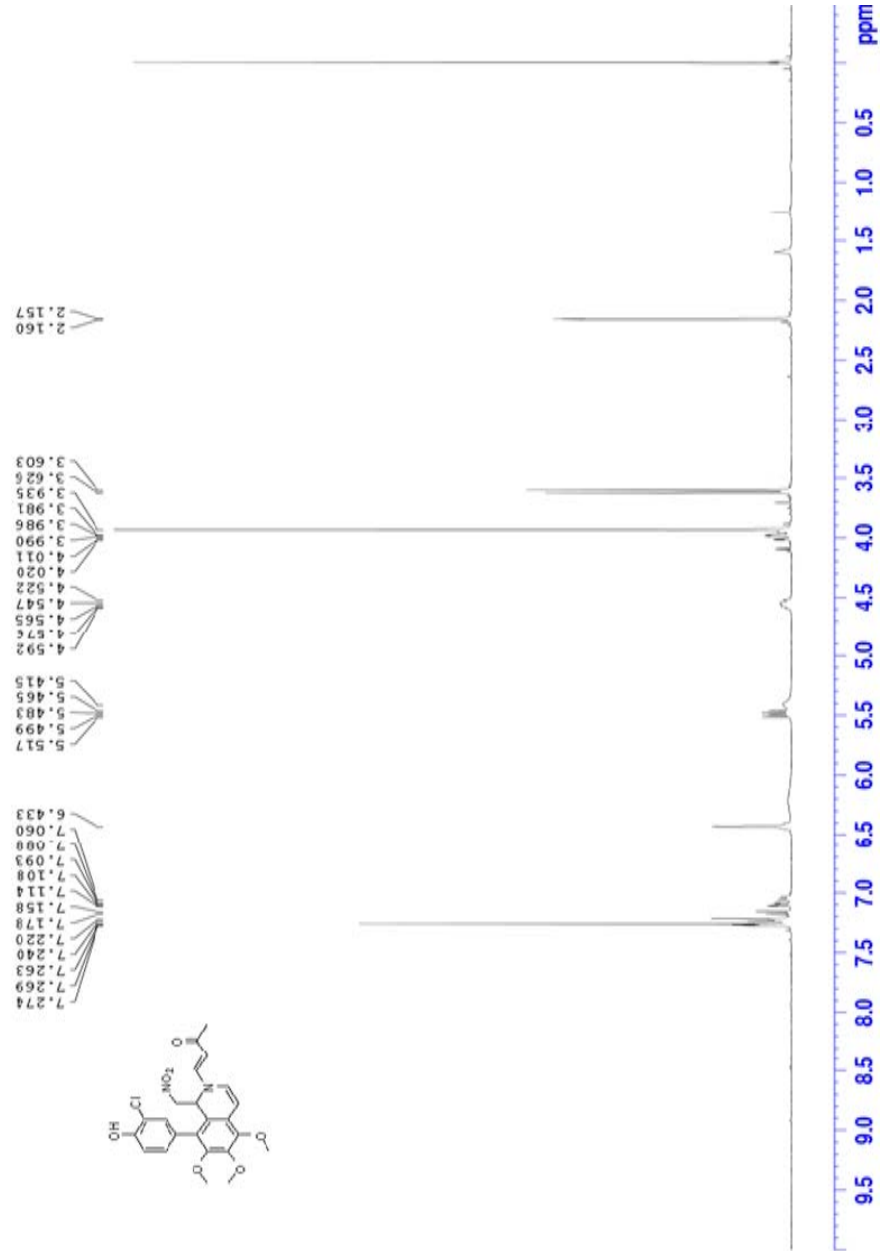
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **6c**



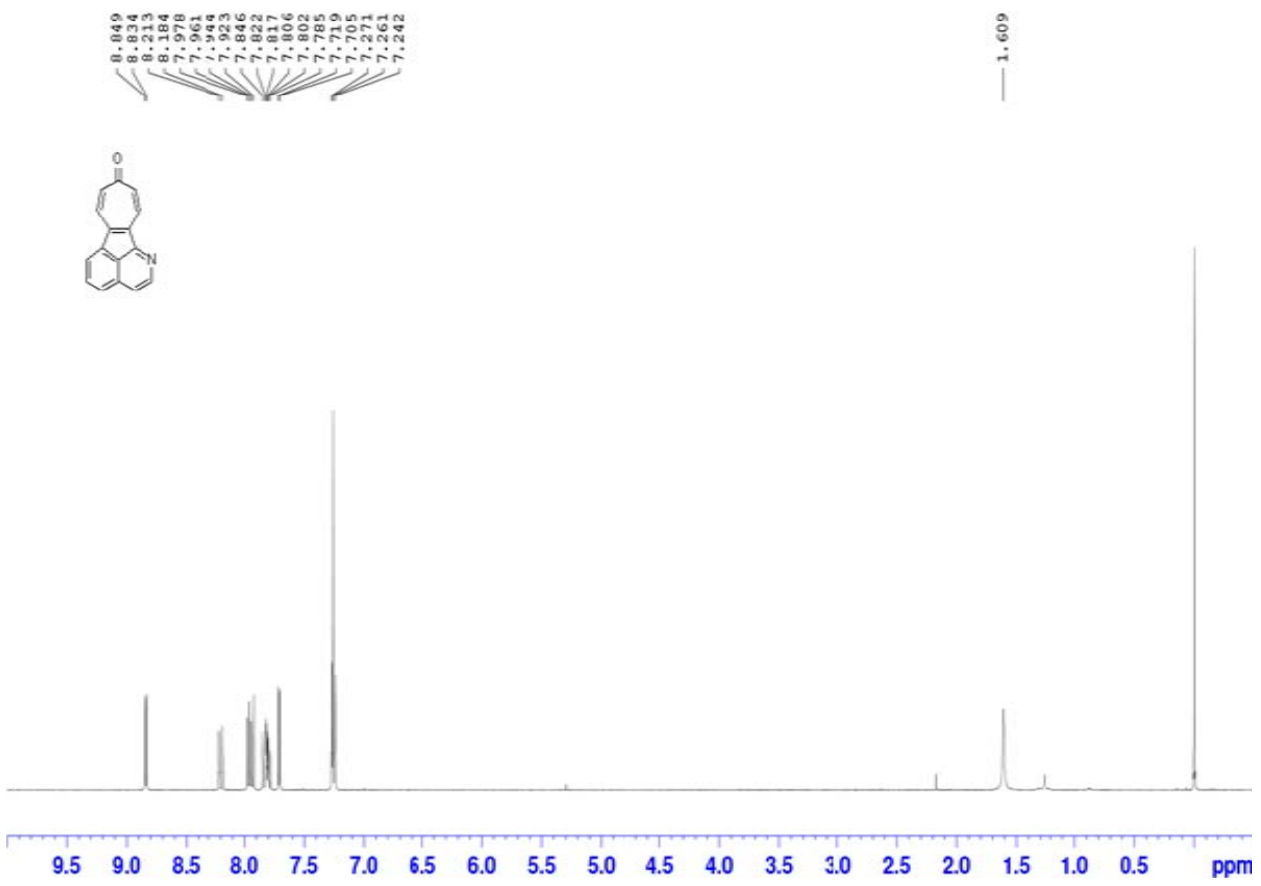
400 MHz ^{1}H-NMR spectrum (DMSO-d_6) of compound **6d**



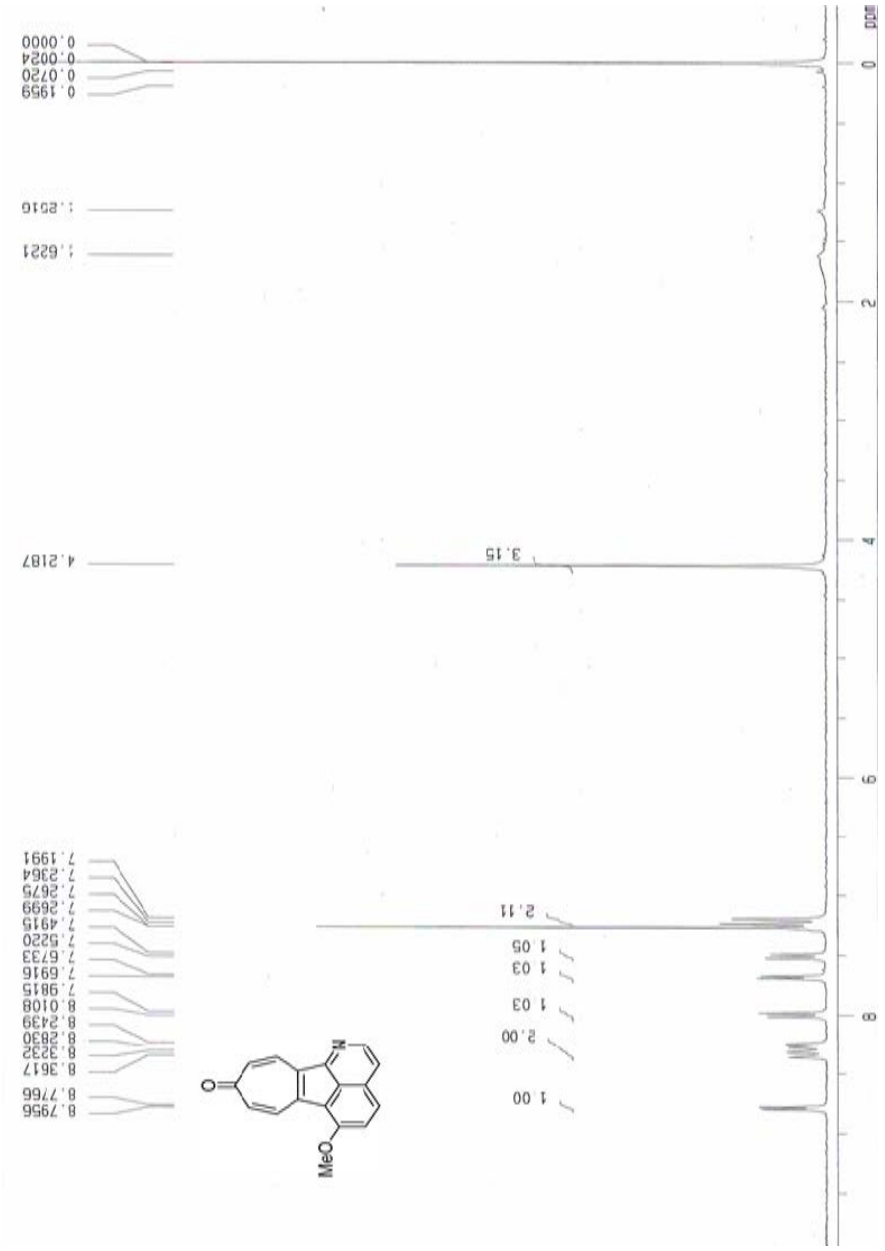
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **9c**



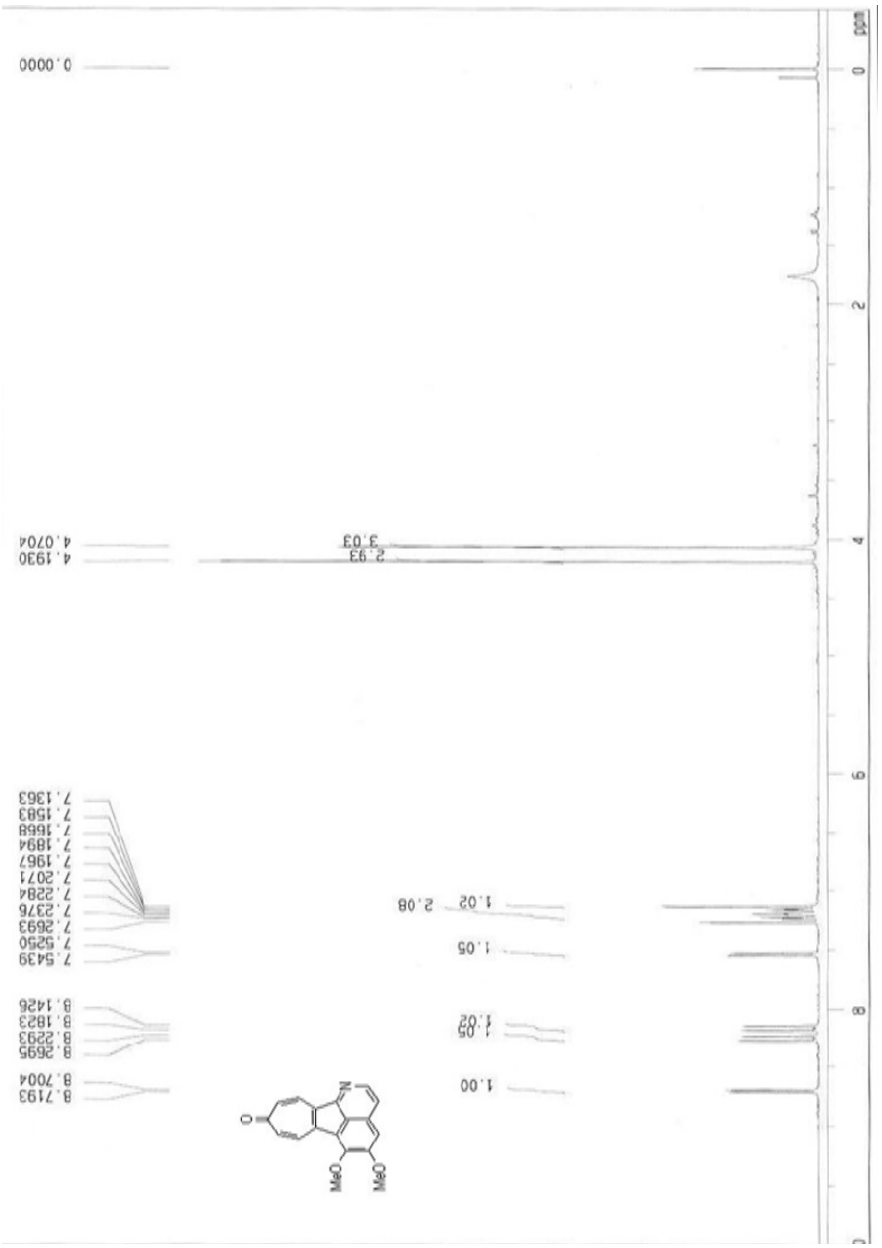
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **9d**



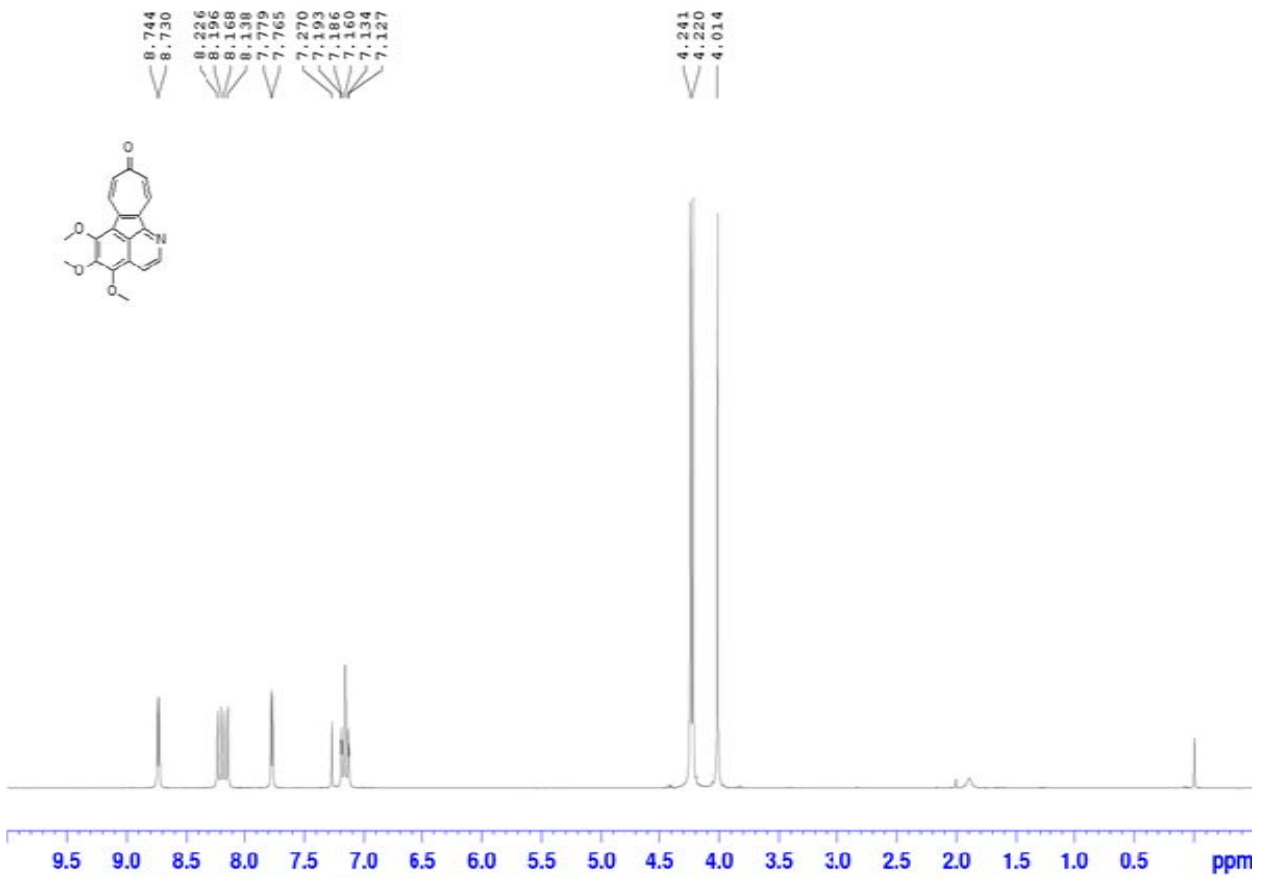
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1a**



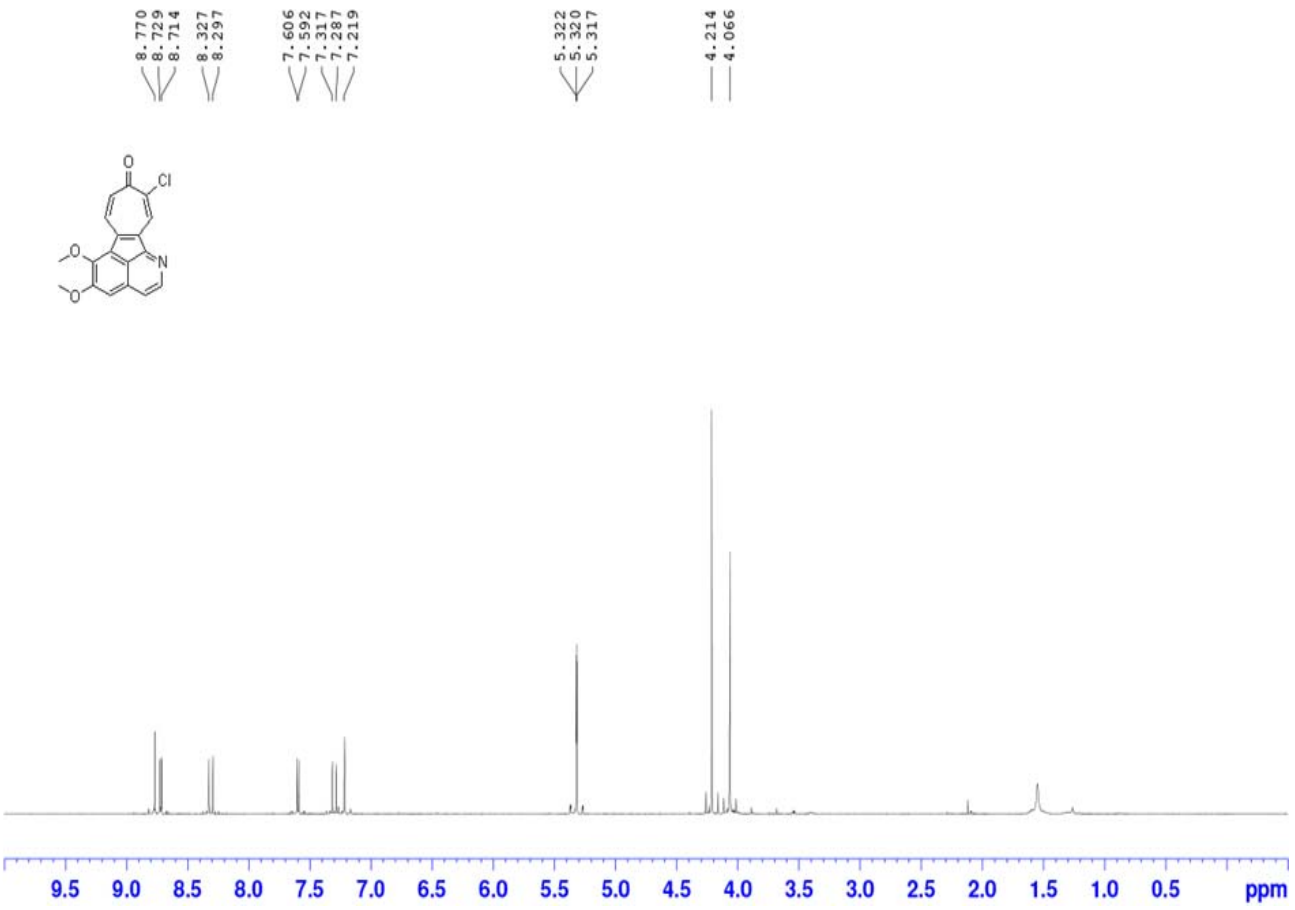
300 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1b**



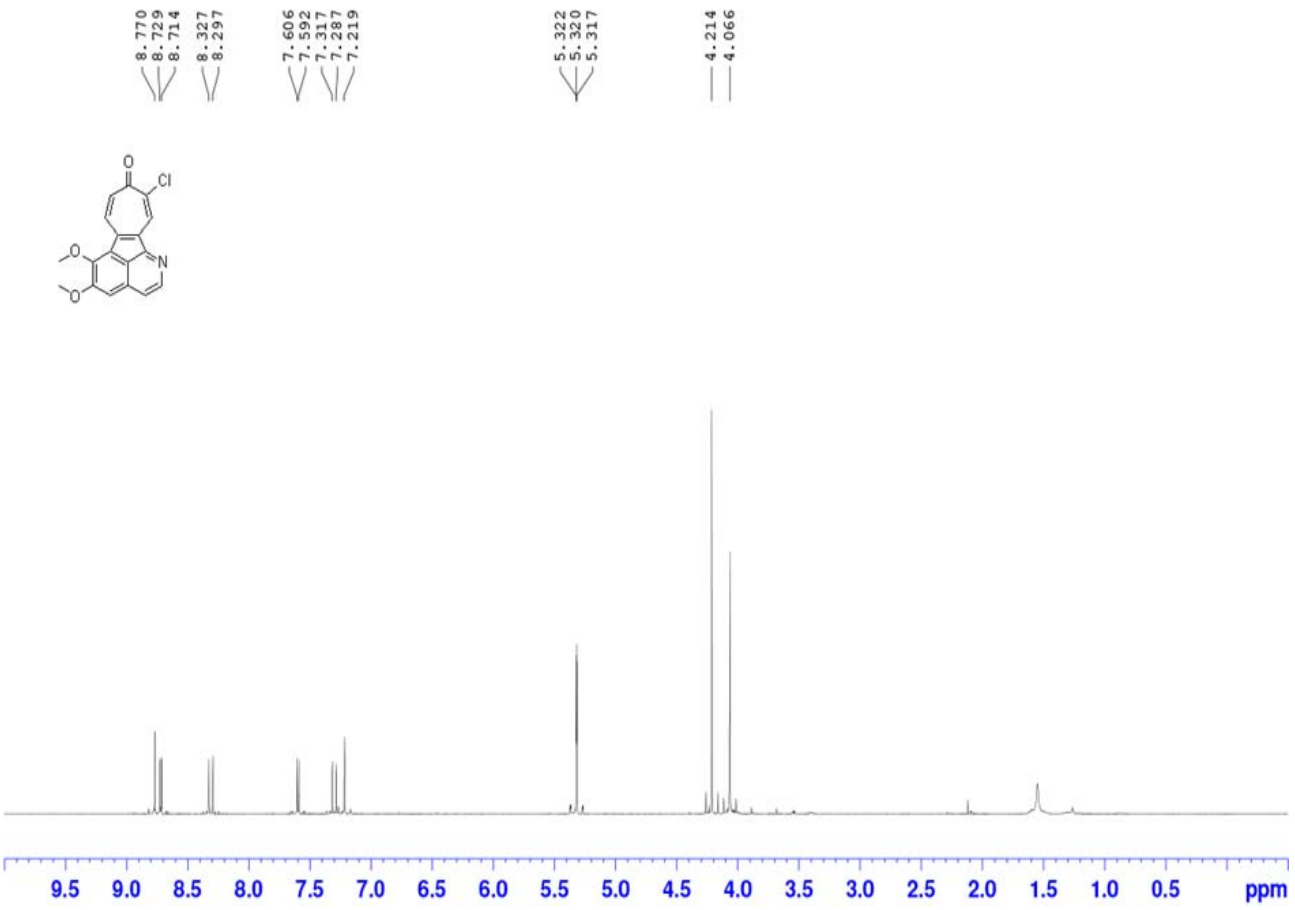
300 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1c**



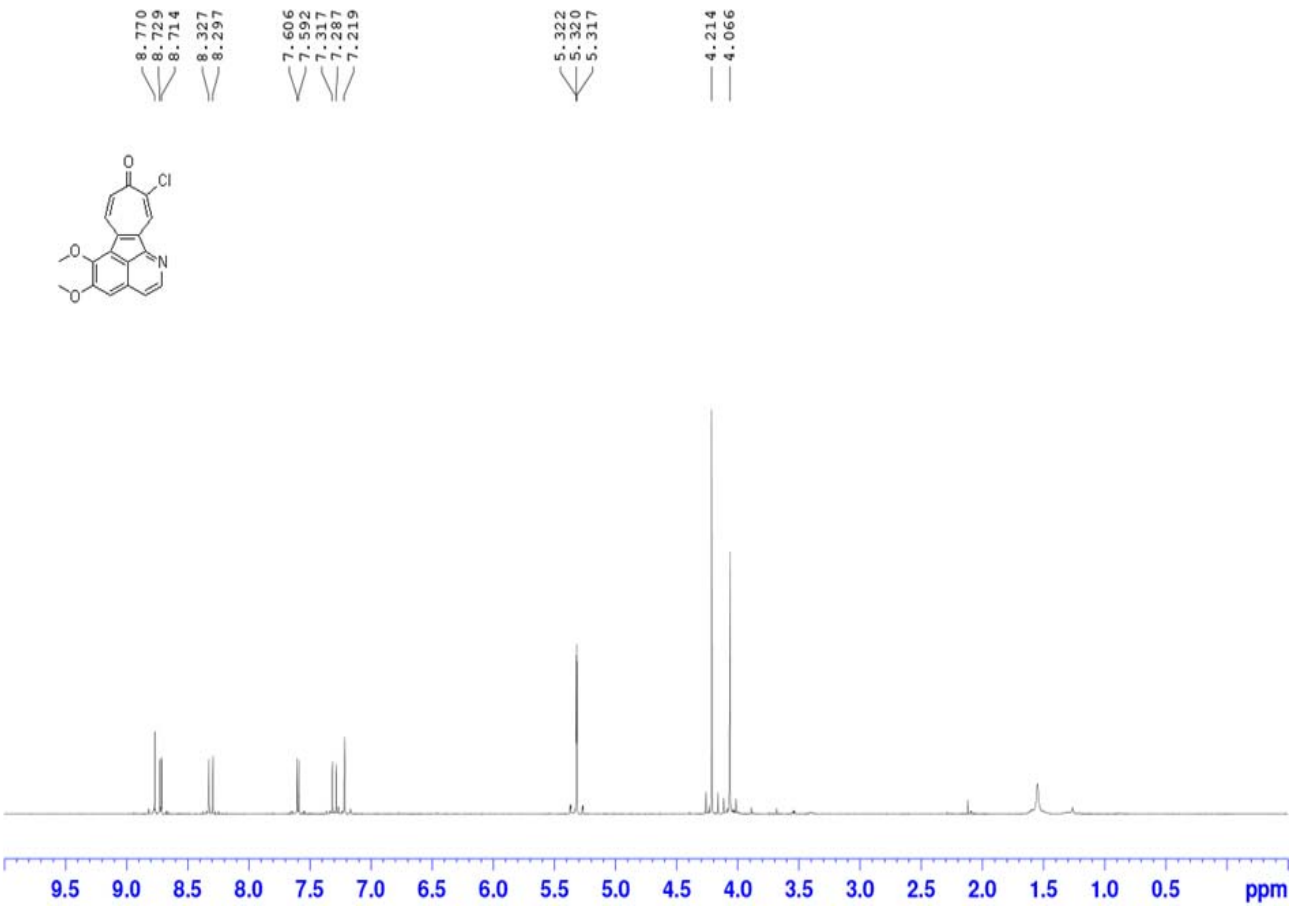
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1d**



400 MHz ^{1}H-NMR spectrum (CD_2Cl_2) of compound **1ca**

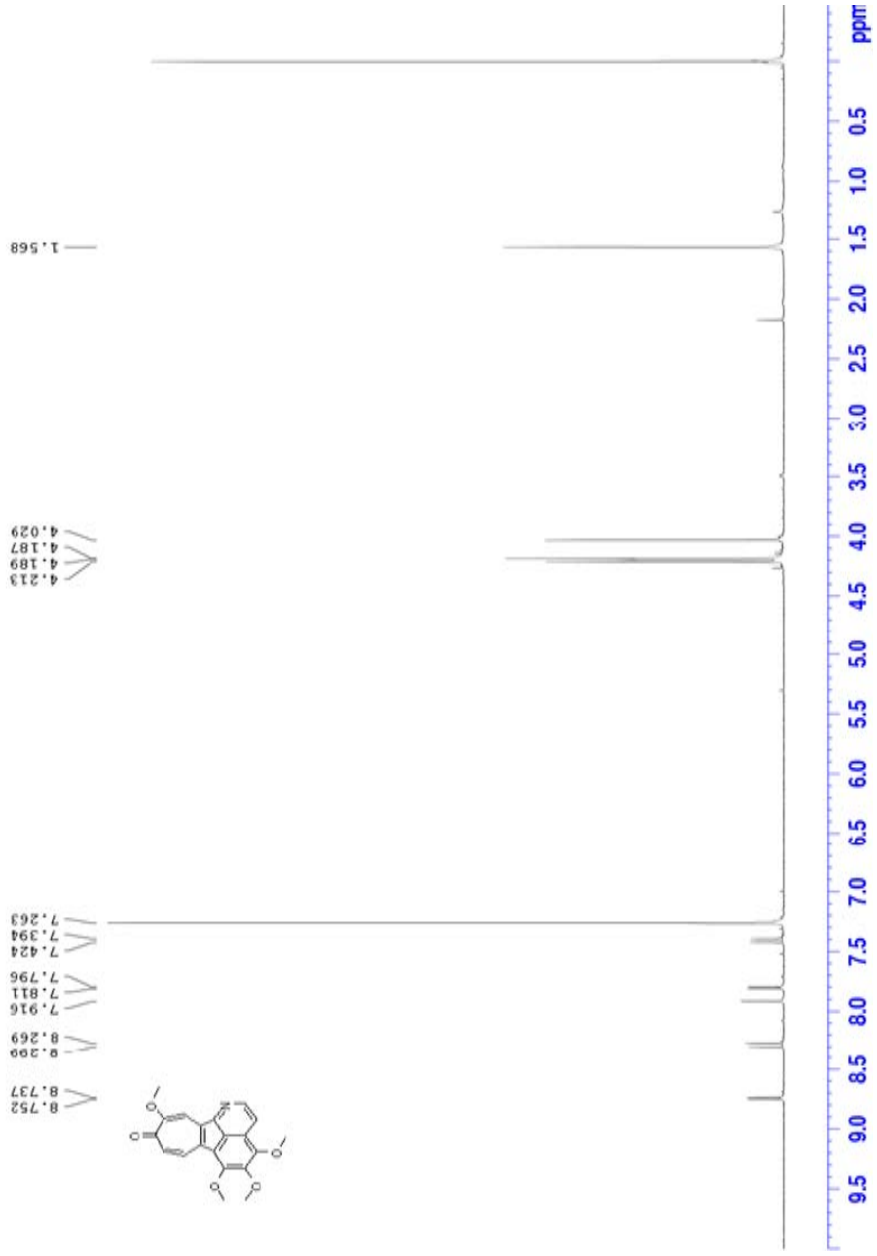


400 MHz ^{1}H-NMR spectrum (CD_2Cl_2) of compound **1cb**

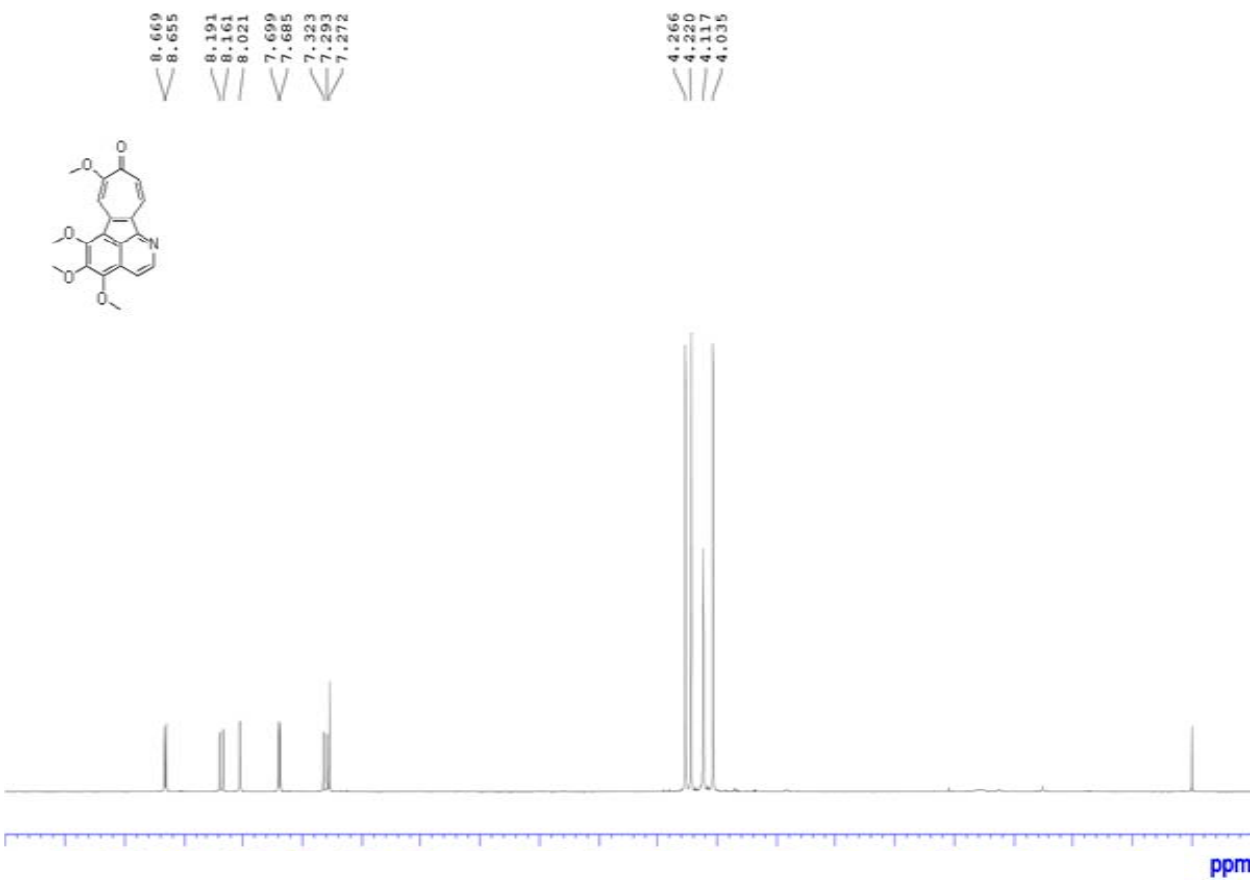


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1da**

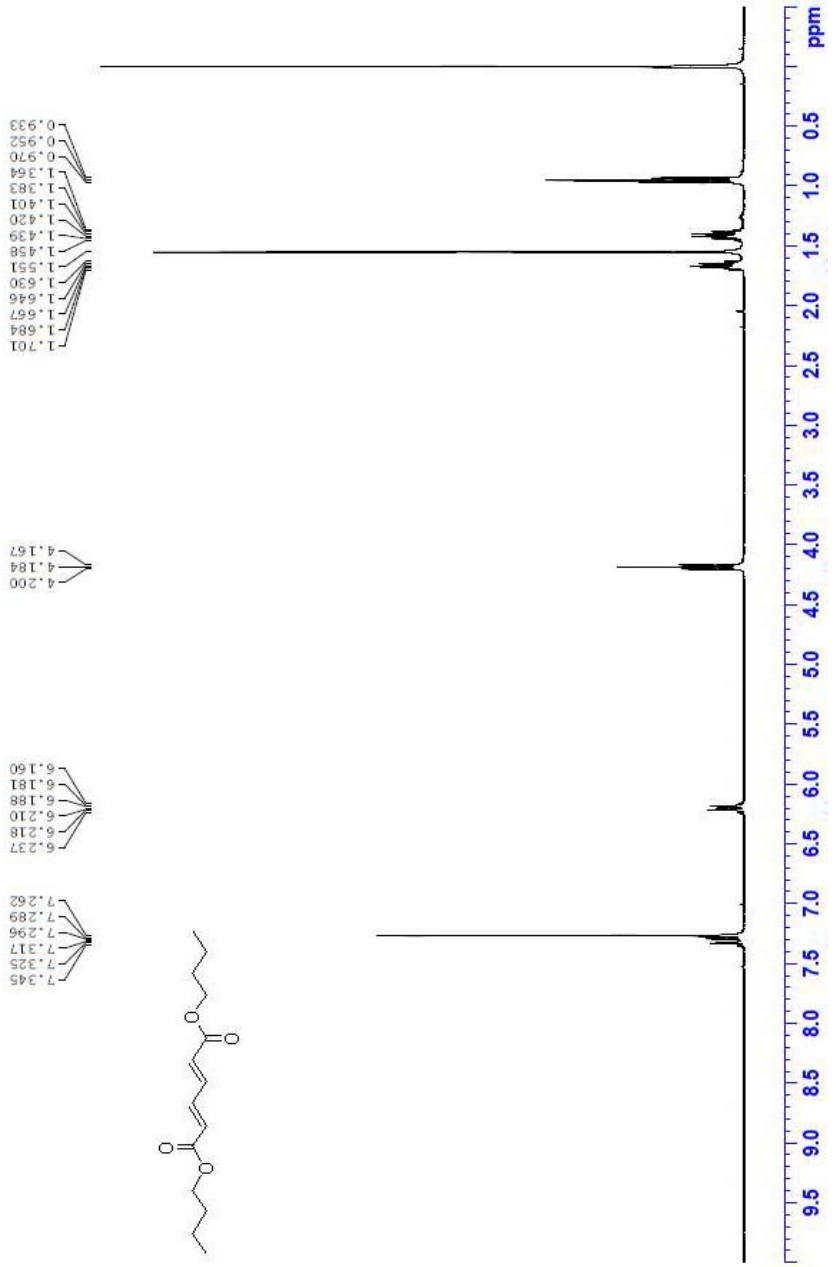
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1db**



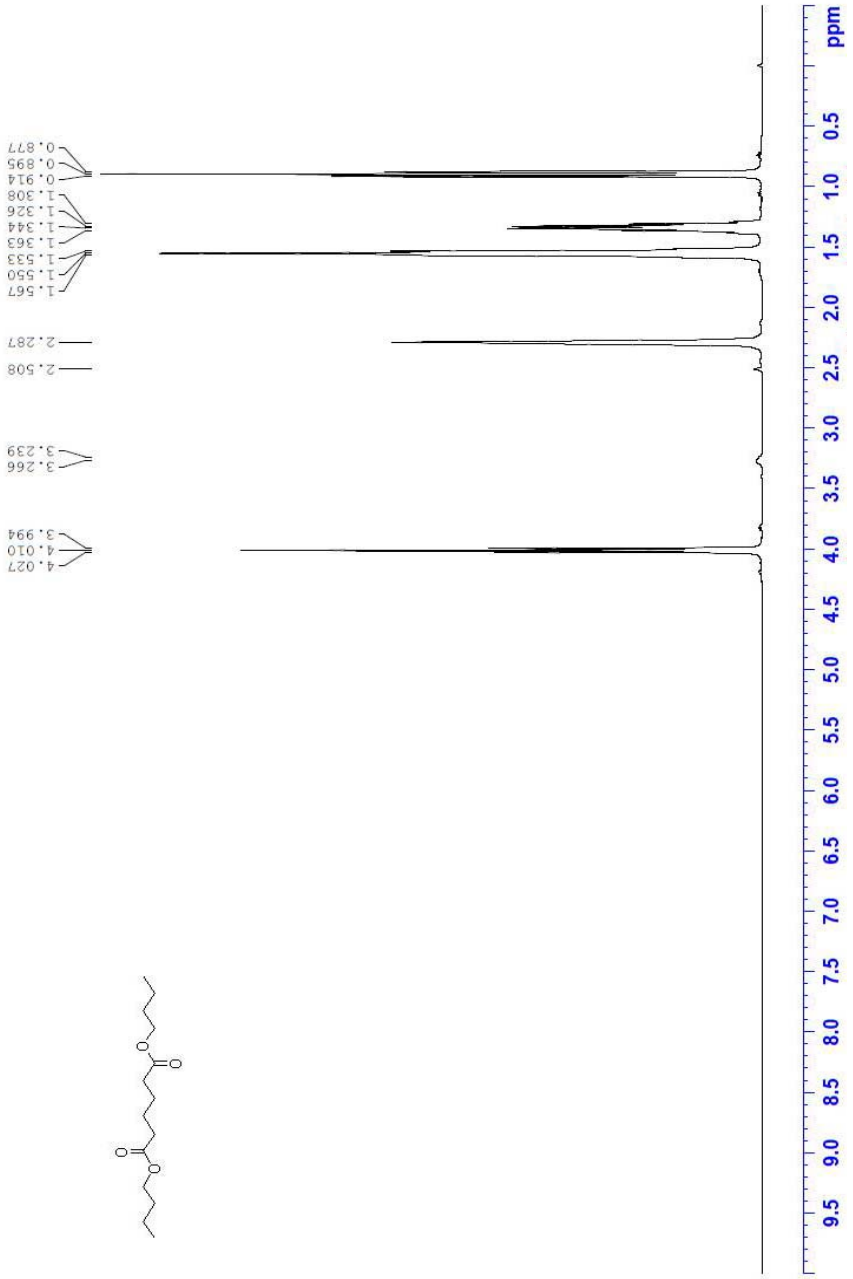
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1dc**



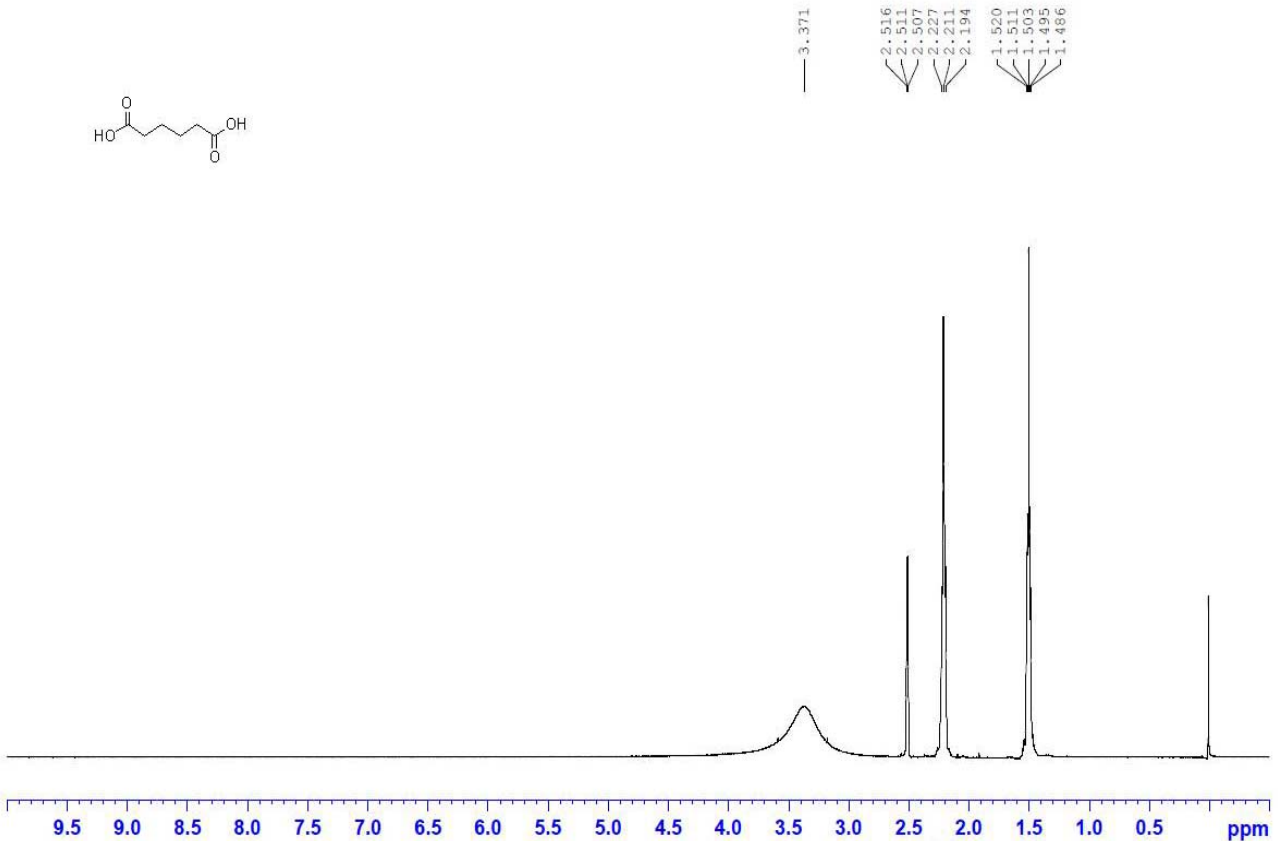
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **1dd**



400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **14a**

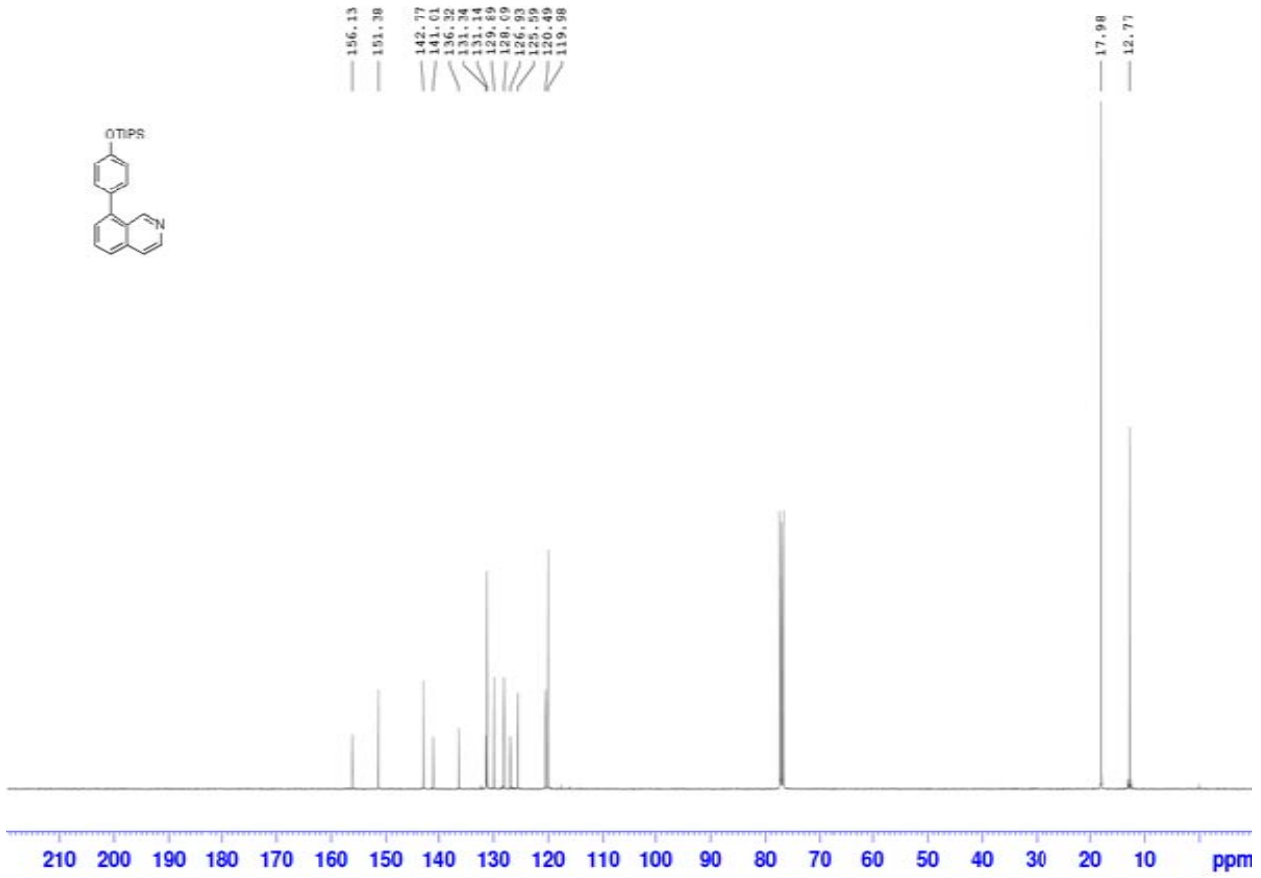


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **15**

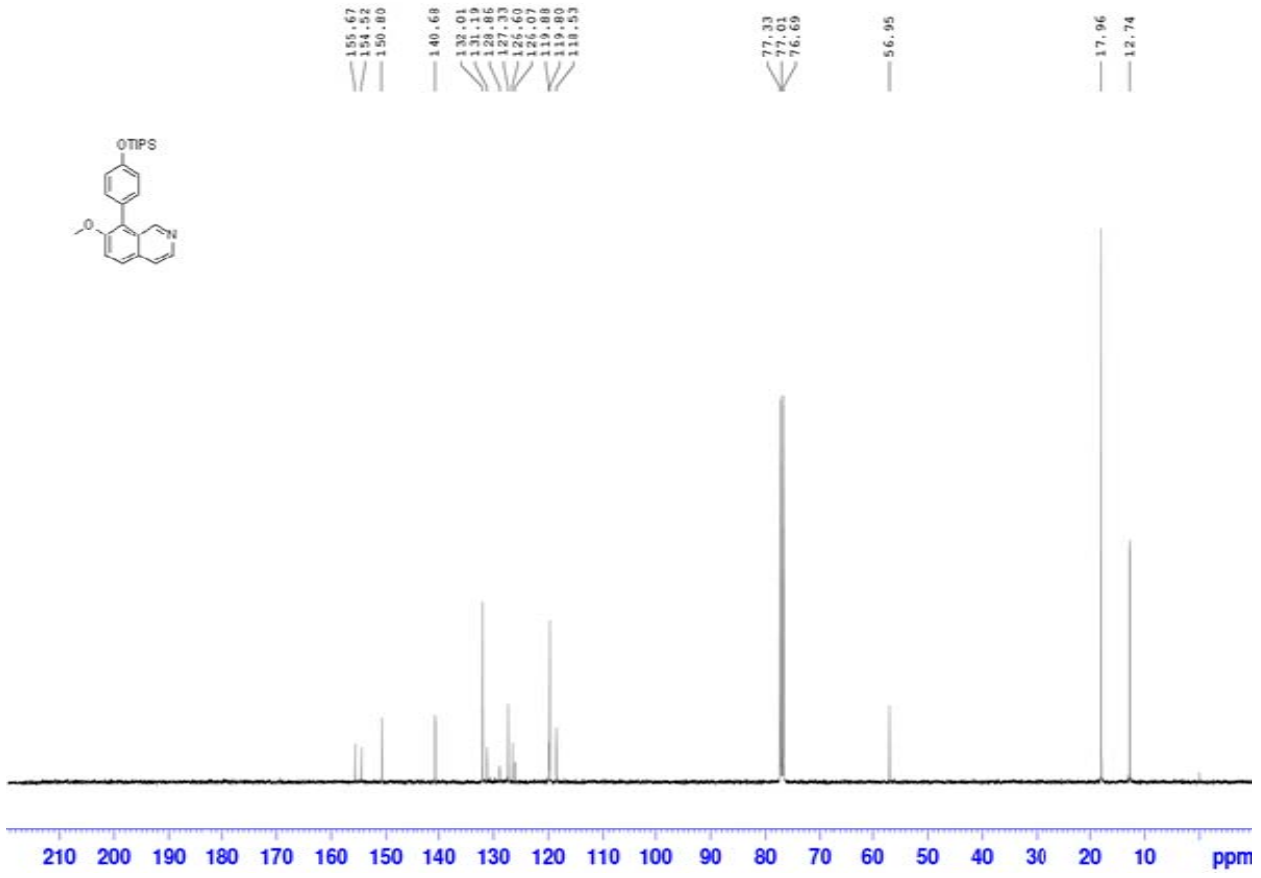


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **16**

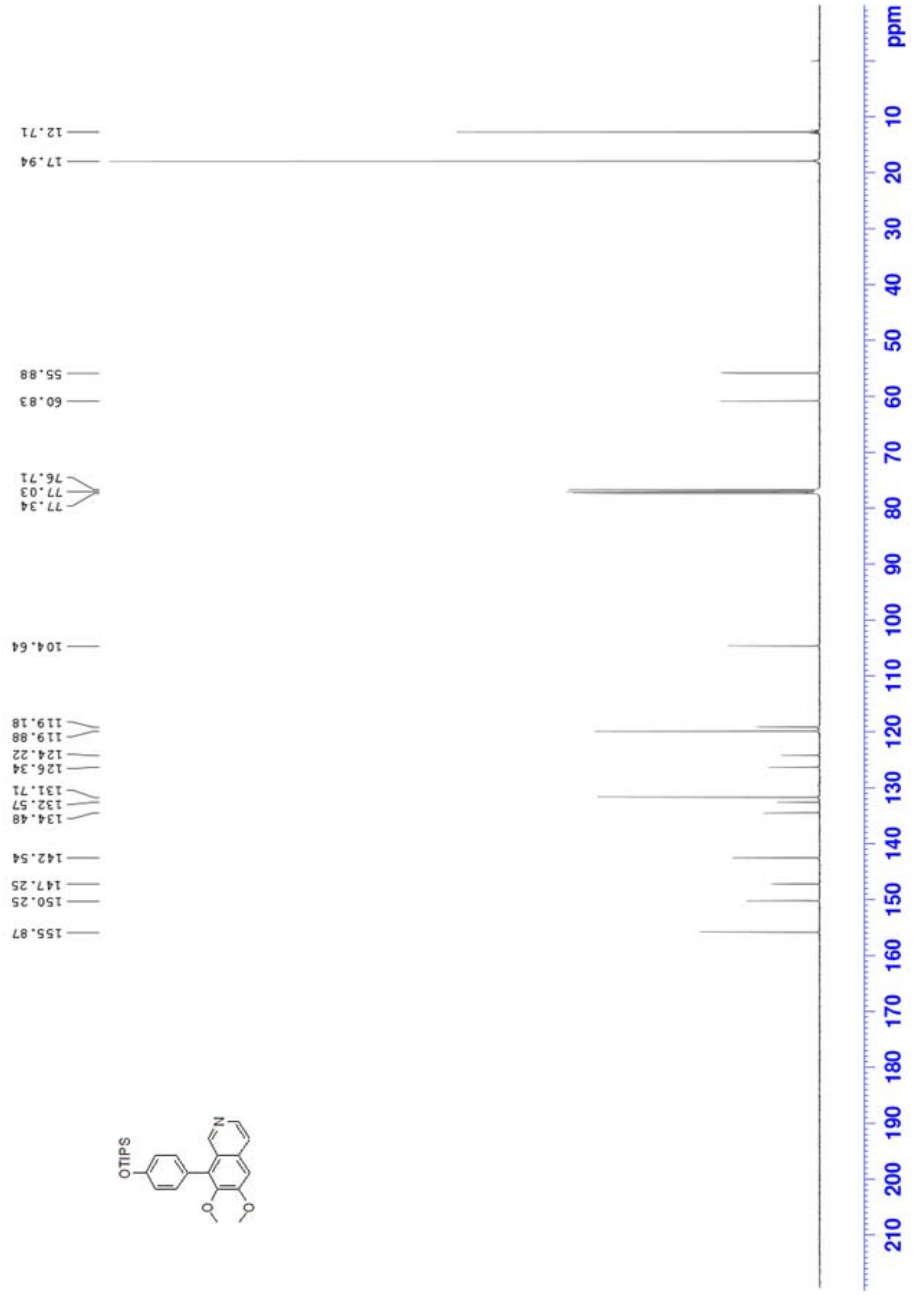
List of ^{13}C-NMR Spectra of Selected Compounds



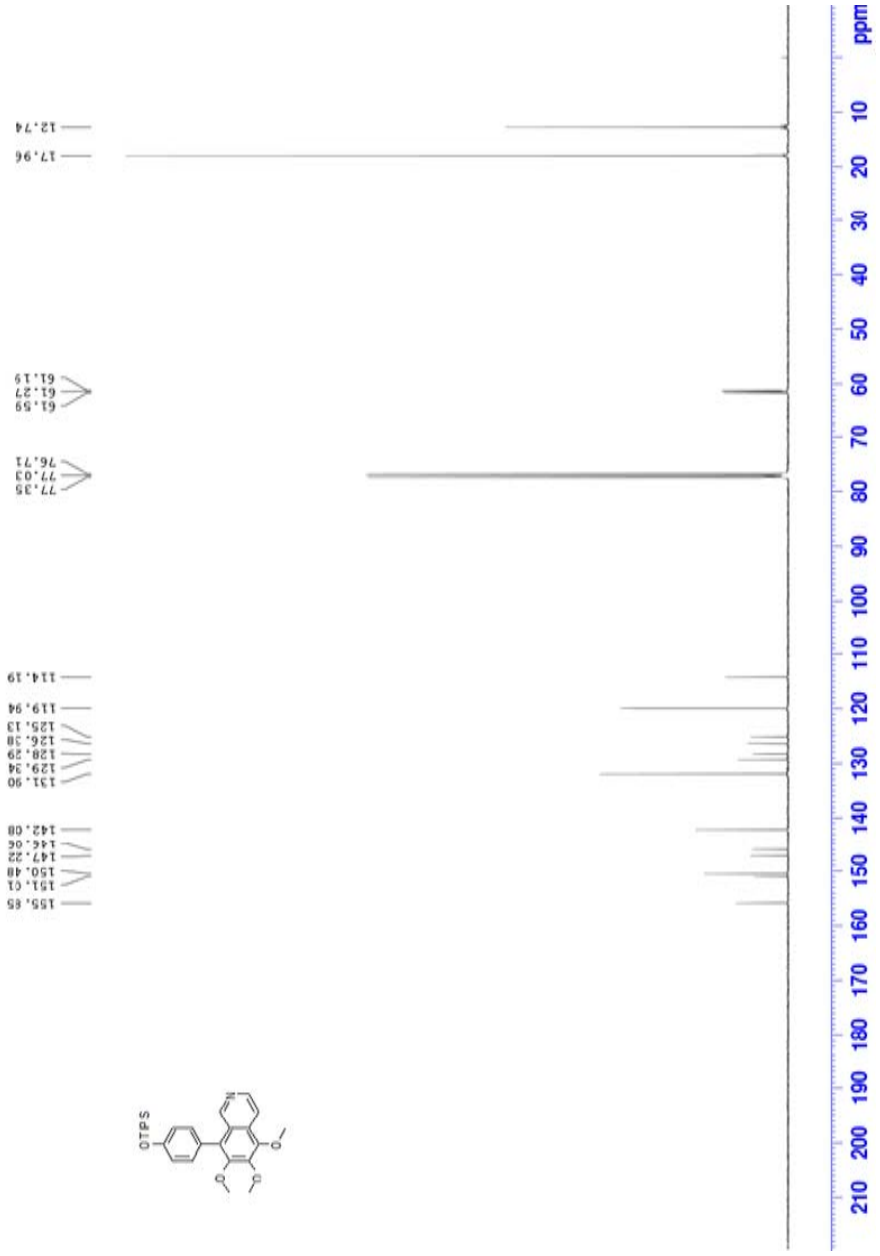
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **4a**



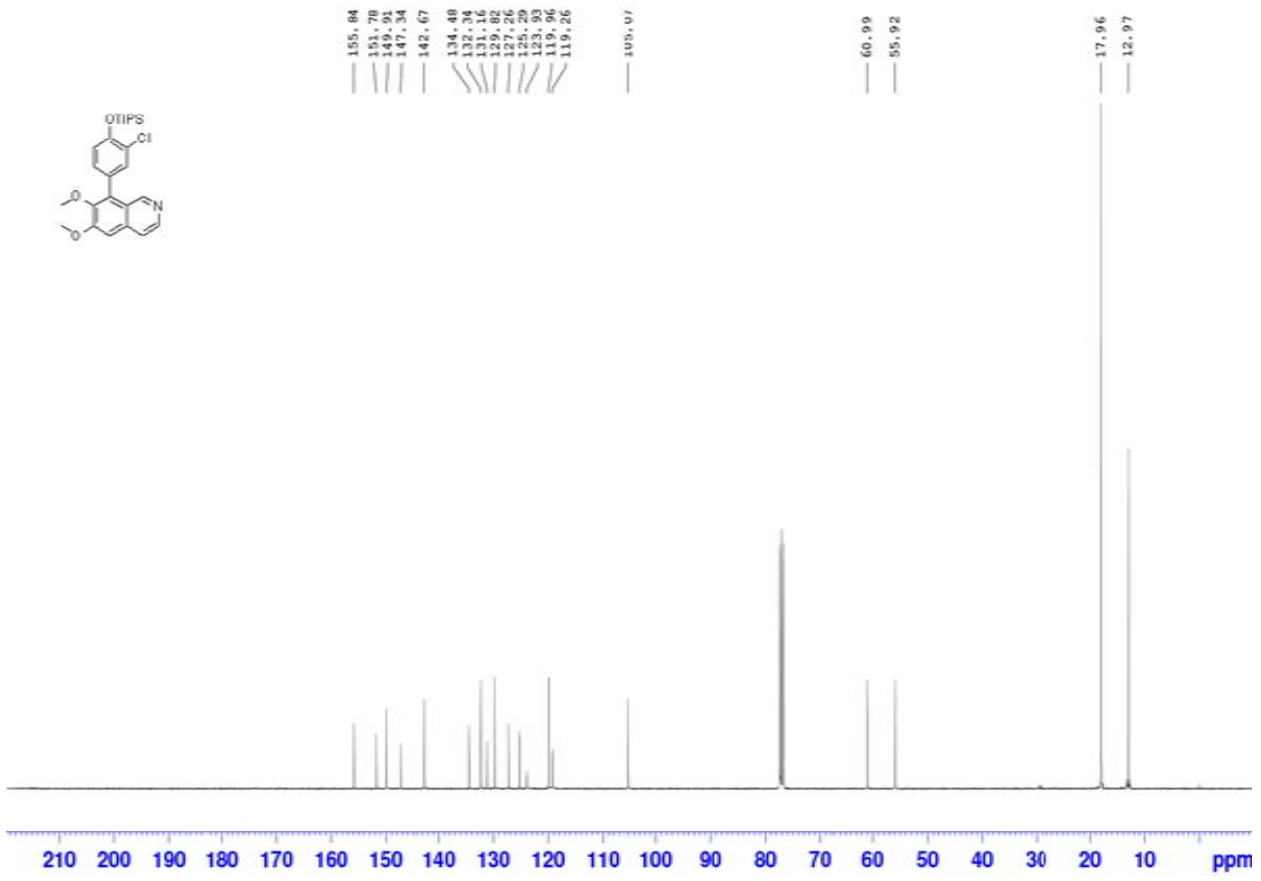
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **4b**



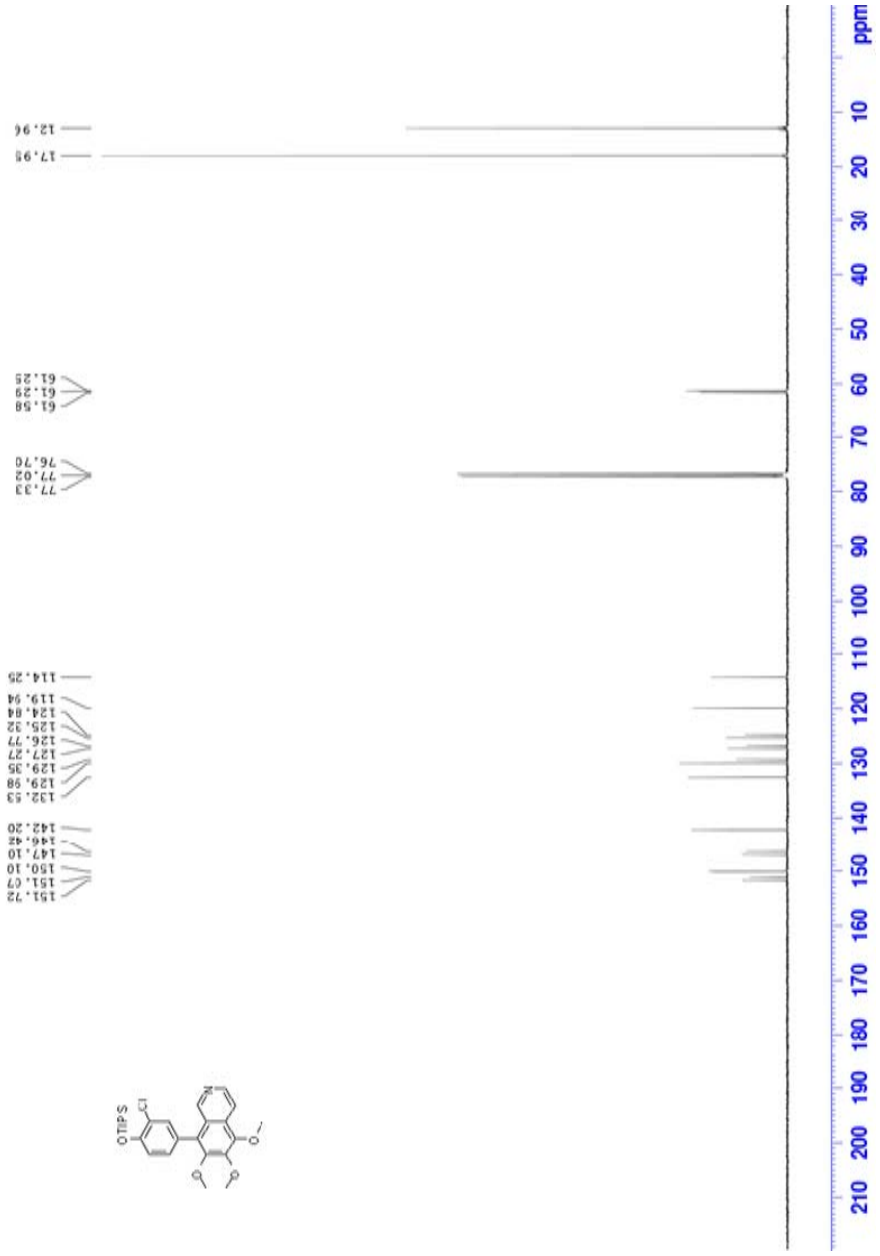
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **4c**



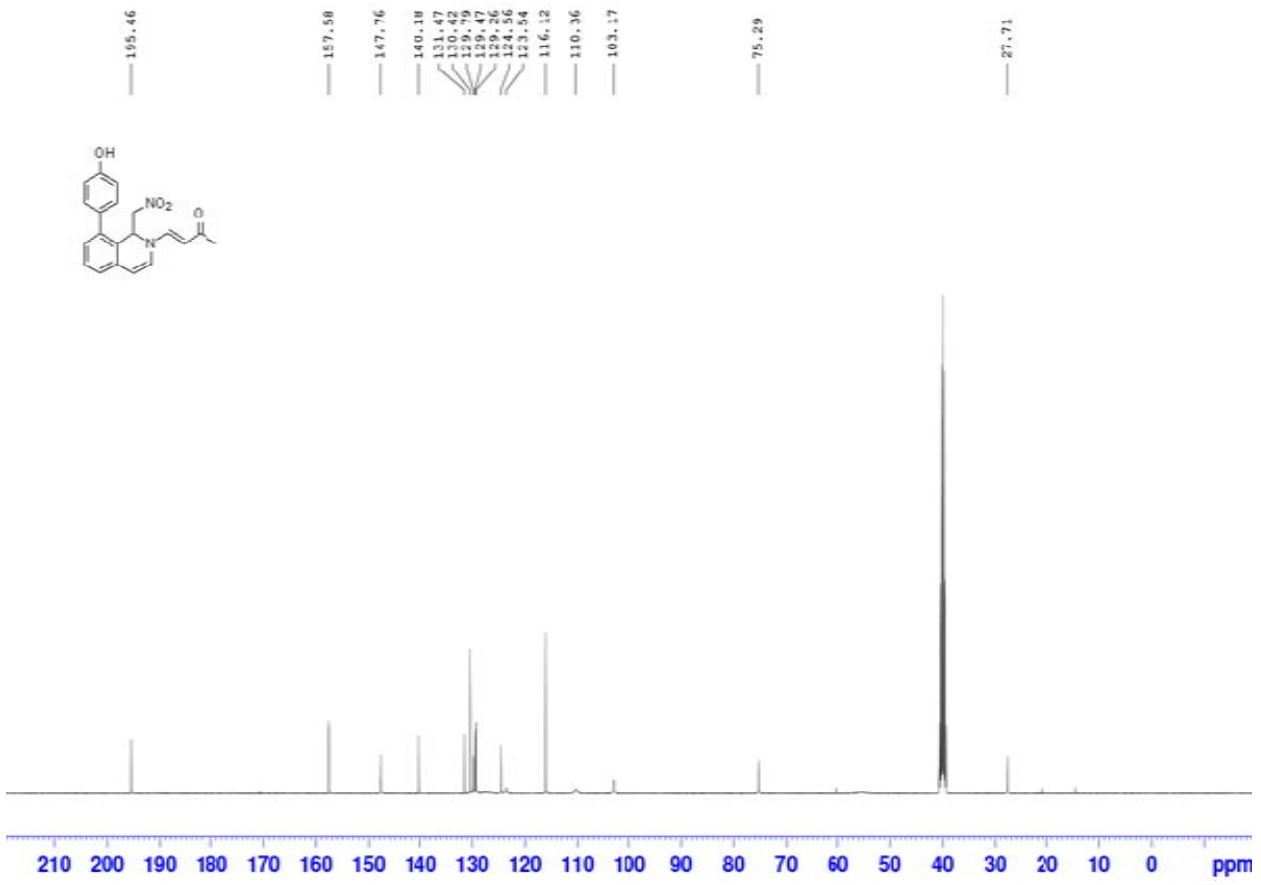
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **4d**



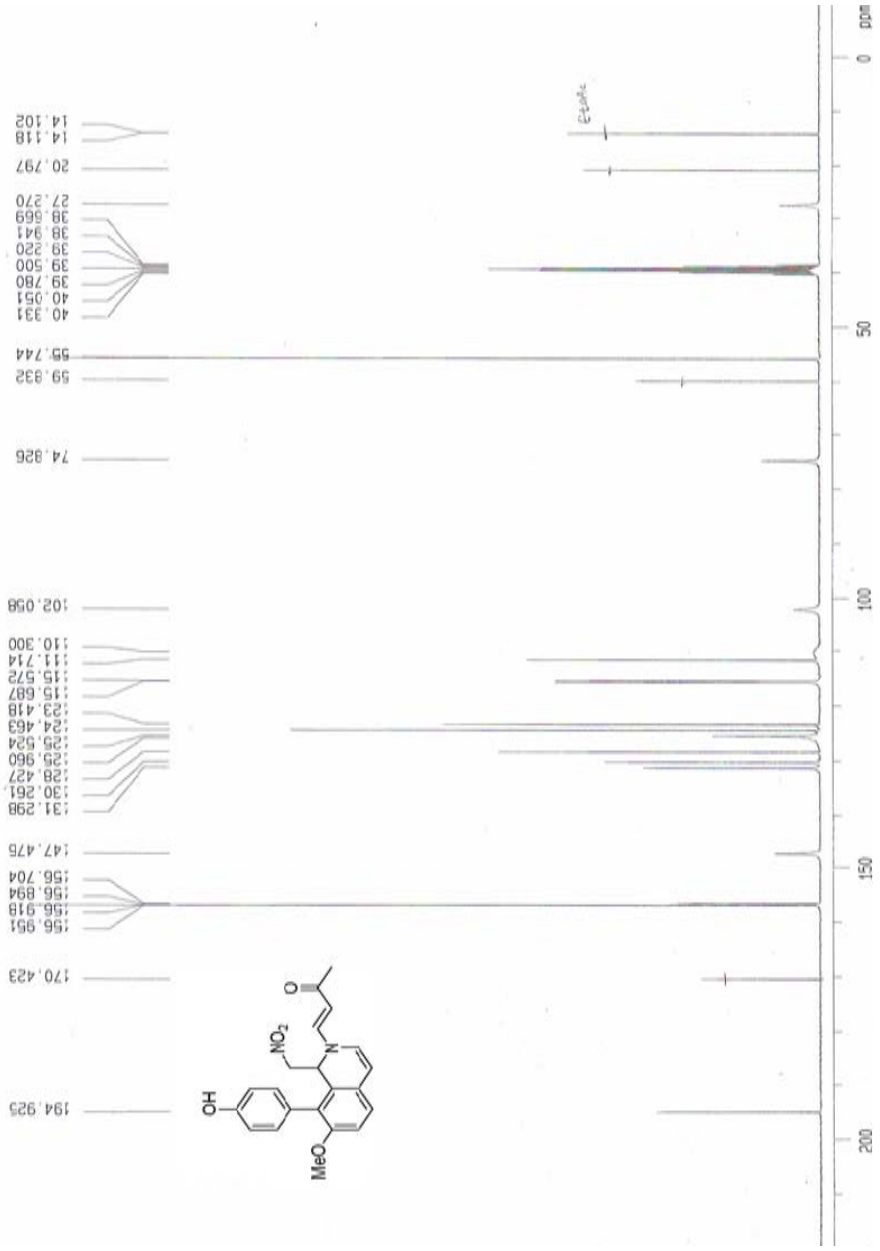
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **7c**



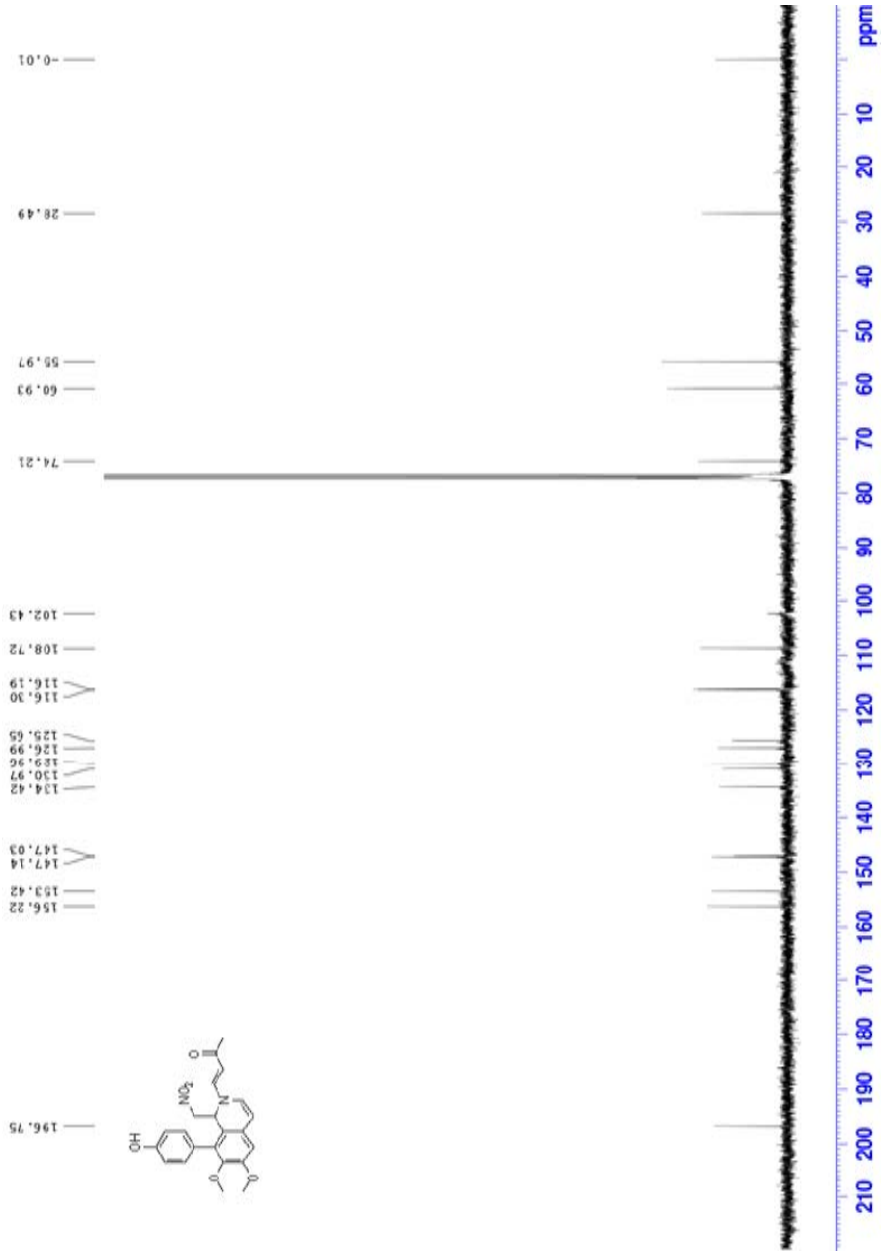
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **7d**



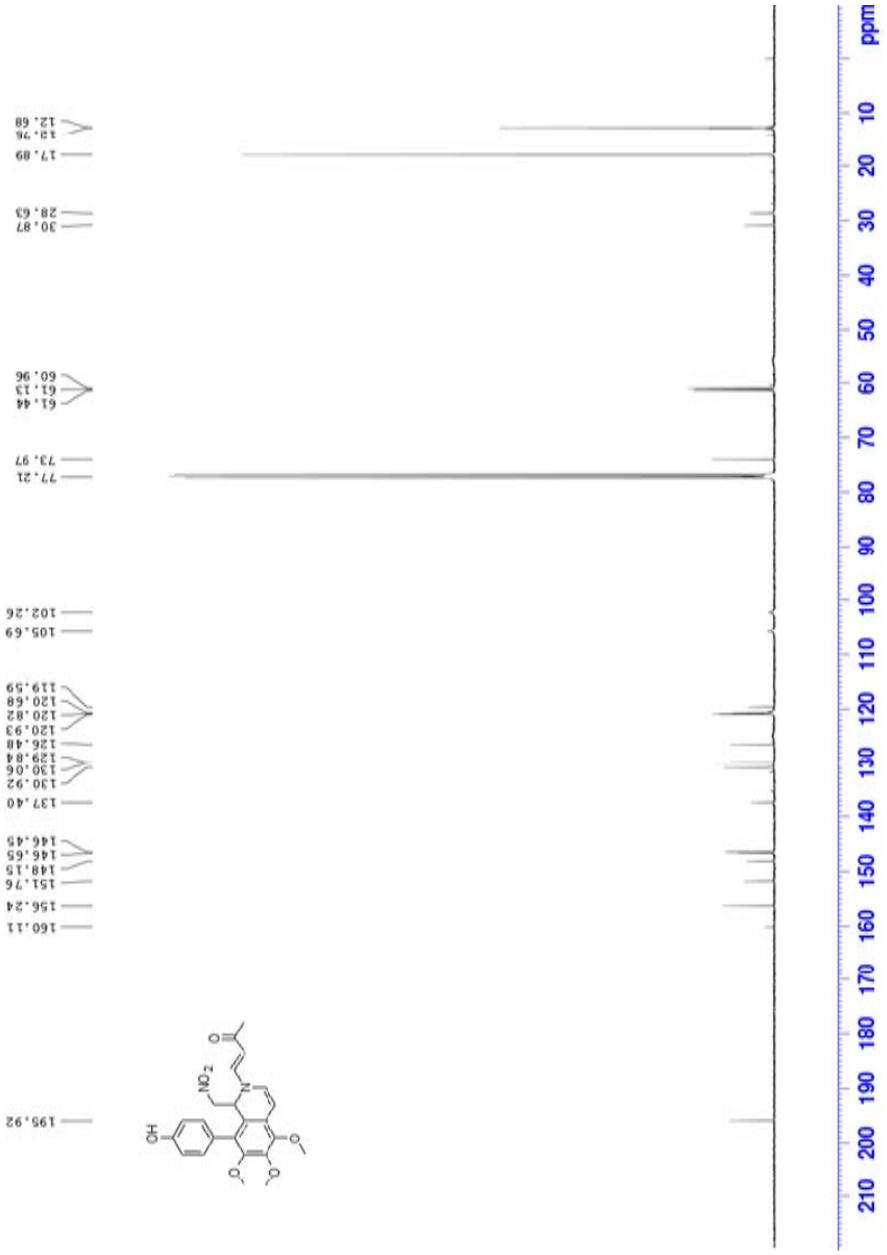
100 MHz ^{13}C-NMR spectrum (DMSO-d_6) of compound **6a**



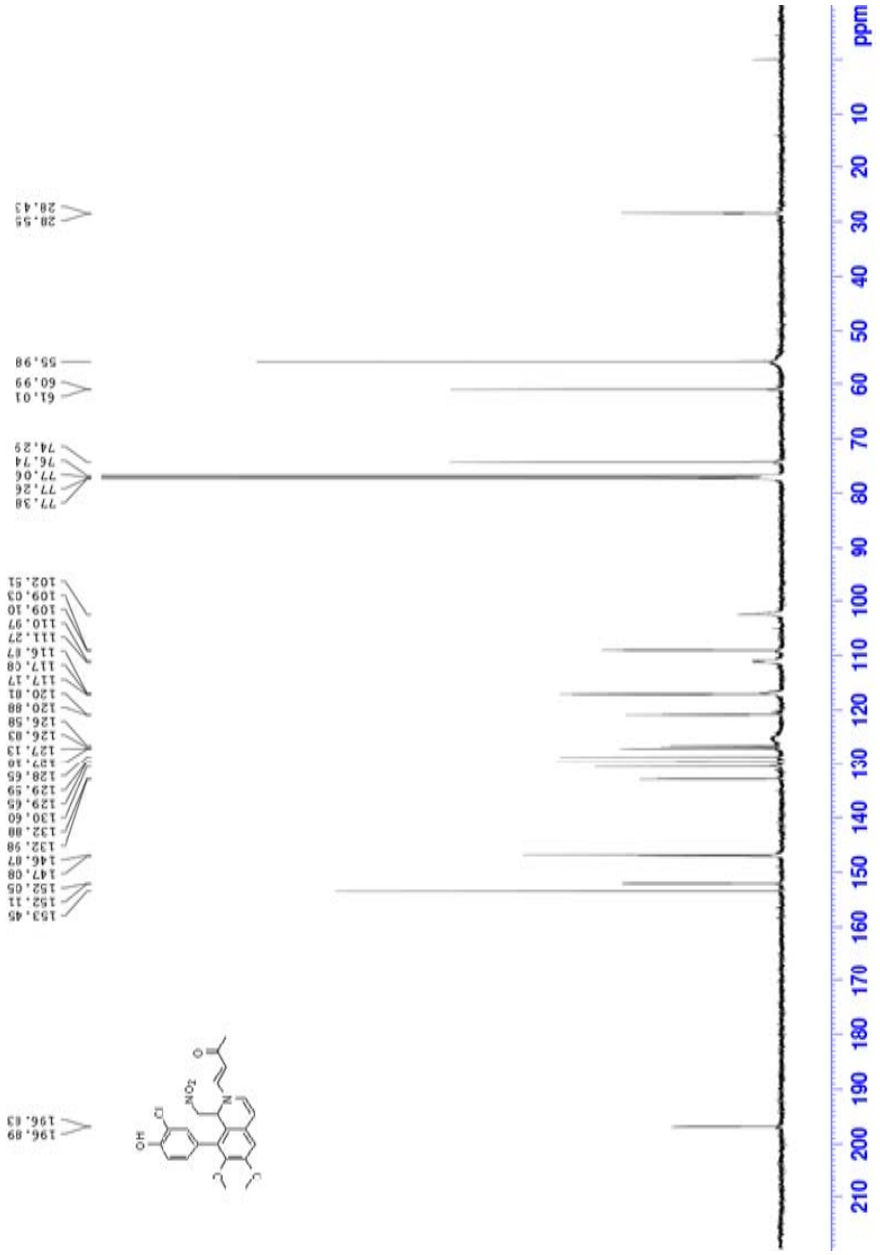
75 MHz ^{13}C-NMR spectrum (DMSO-d$_6$) of compound **6b**



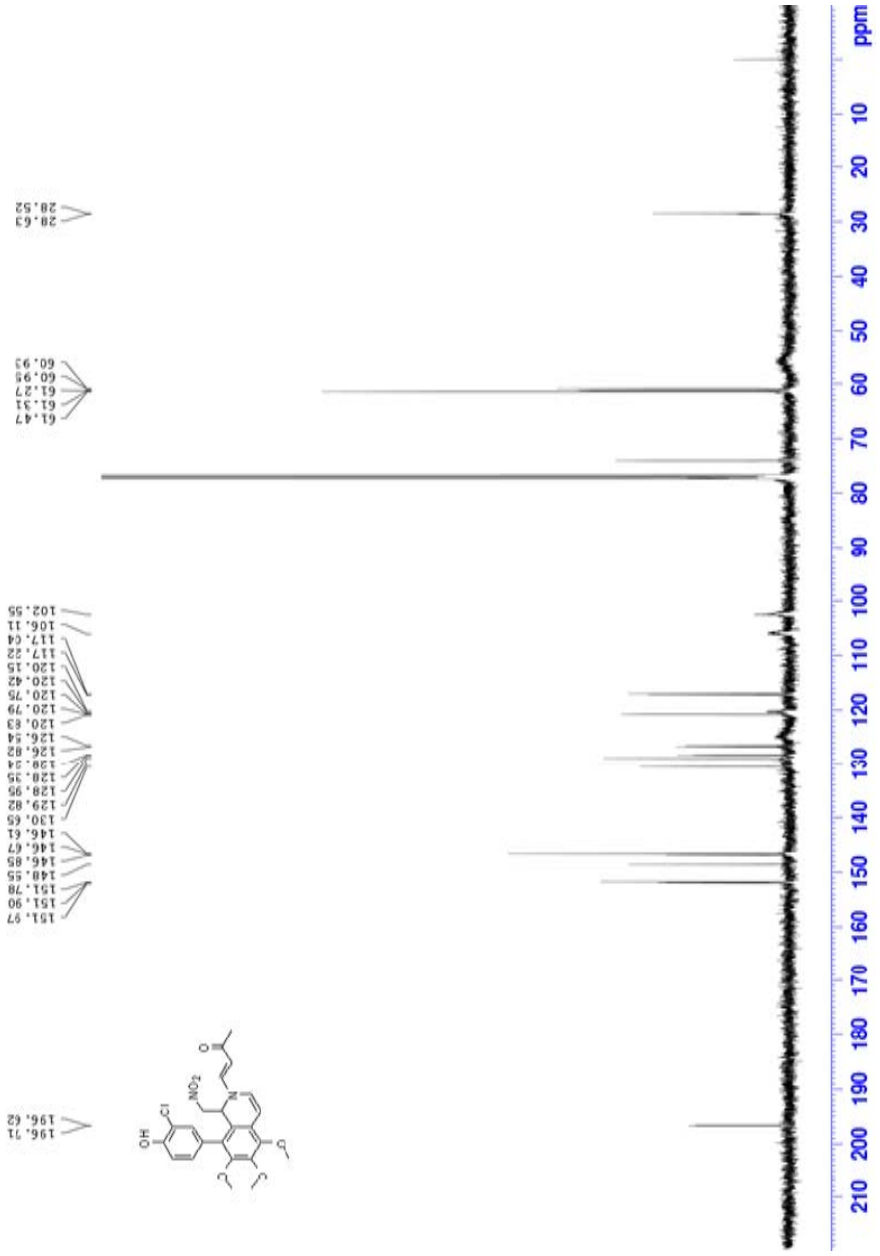
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **6c**



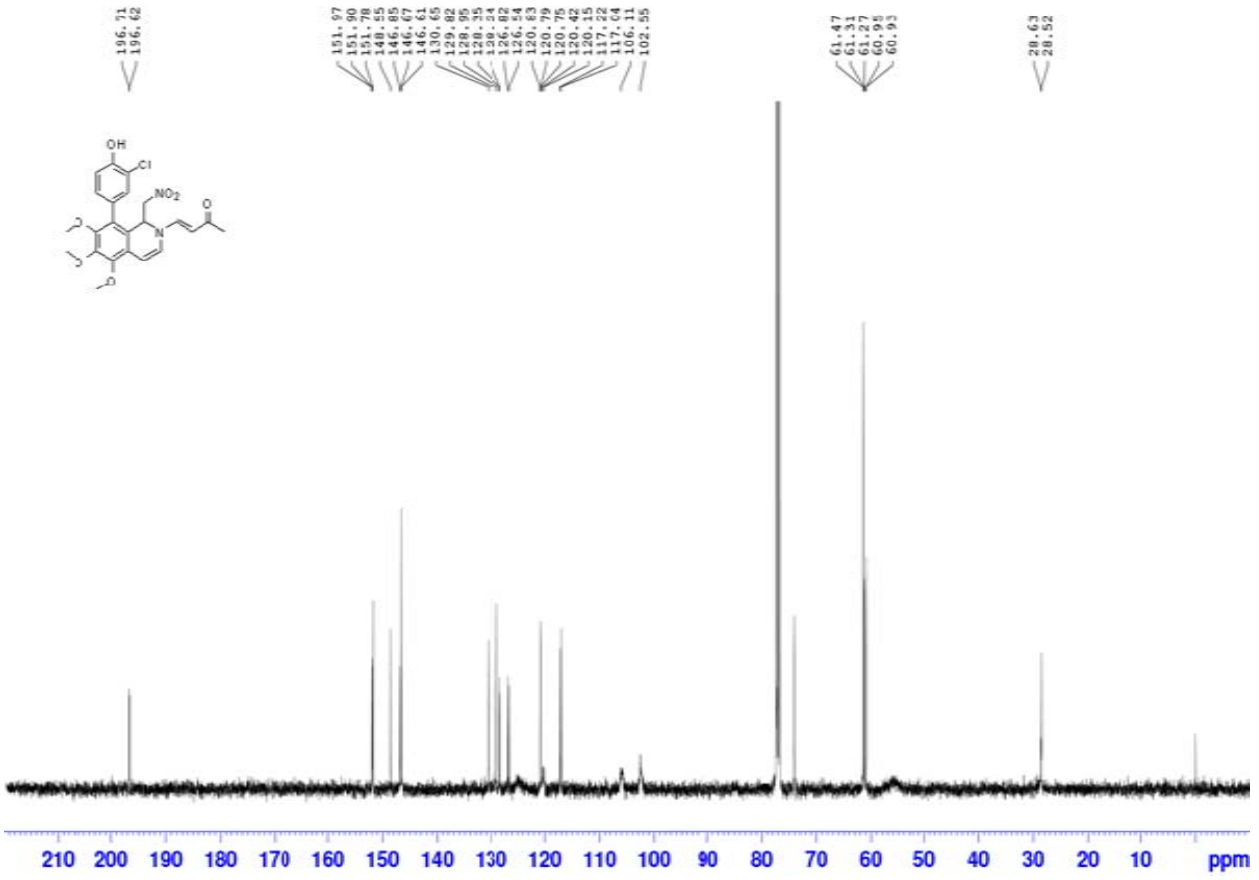
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **6d**



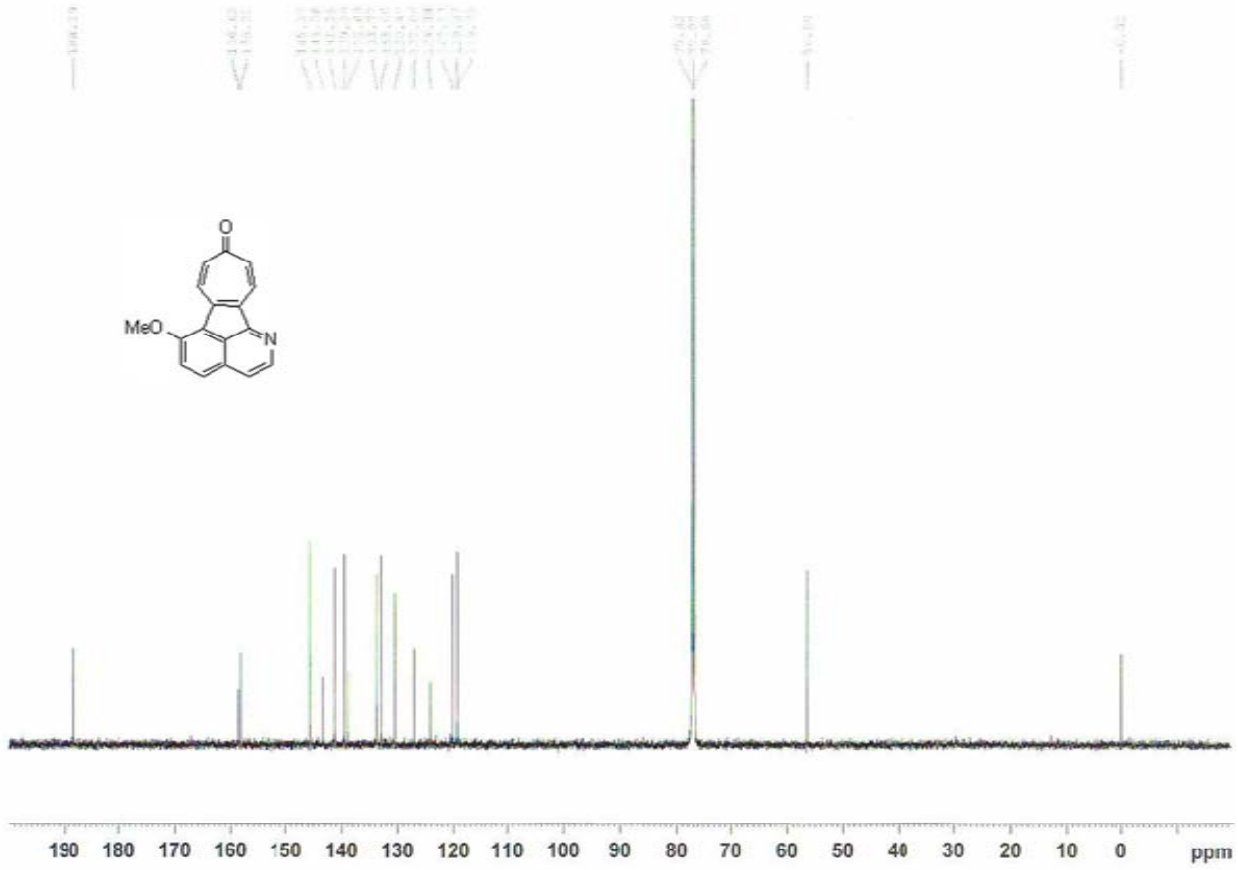
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **9c**



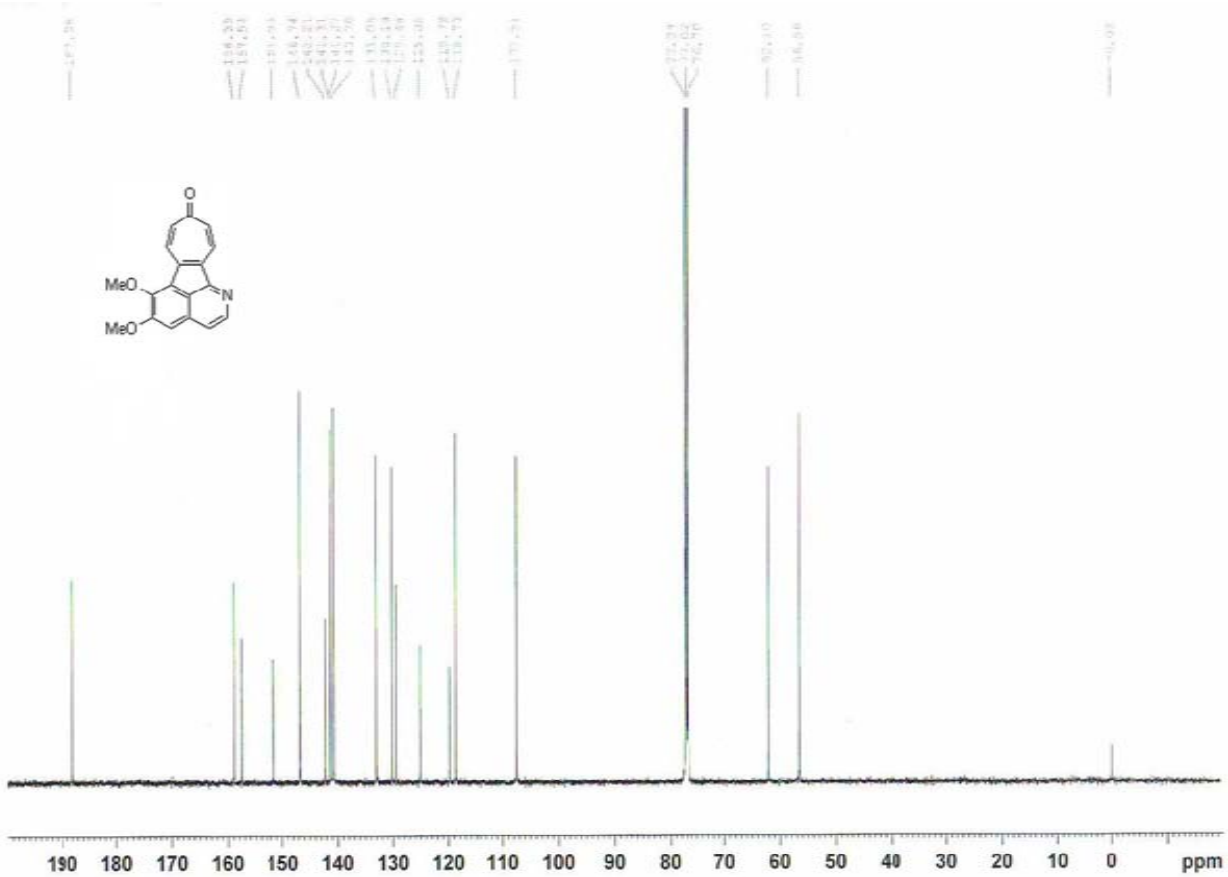
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **9d**



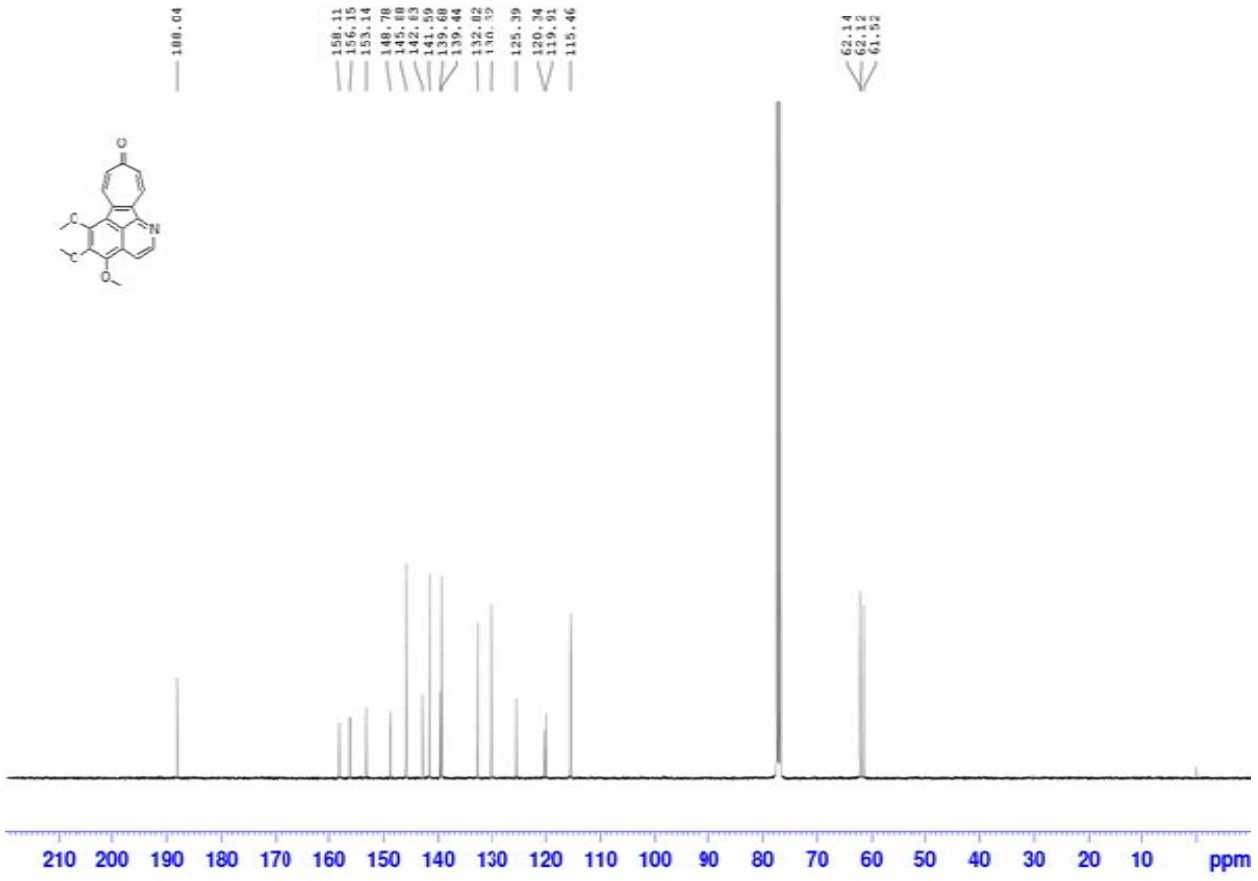
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1a**



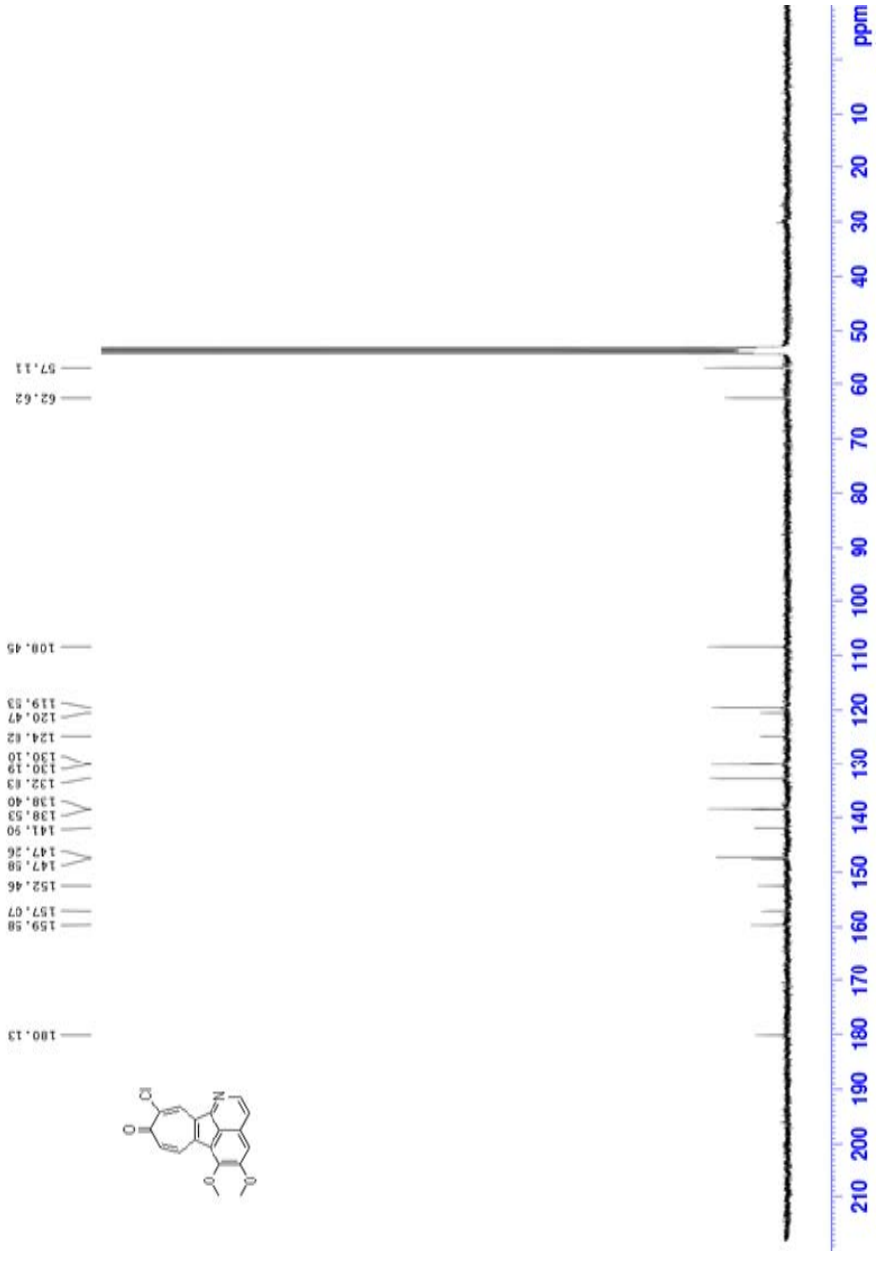
75 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1b**



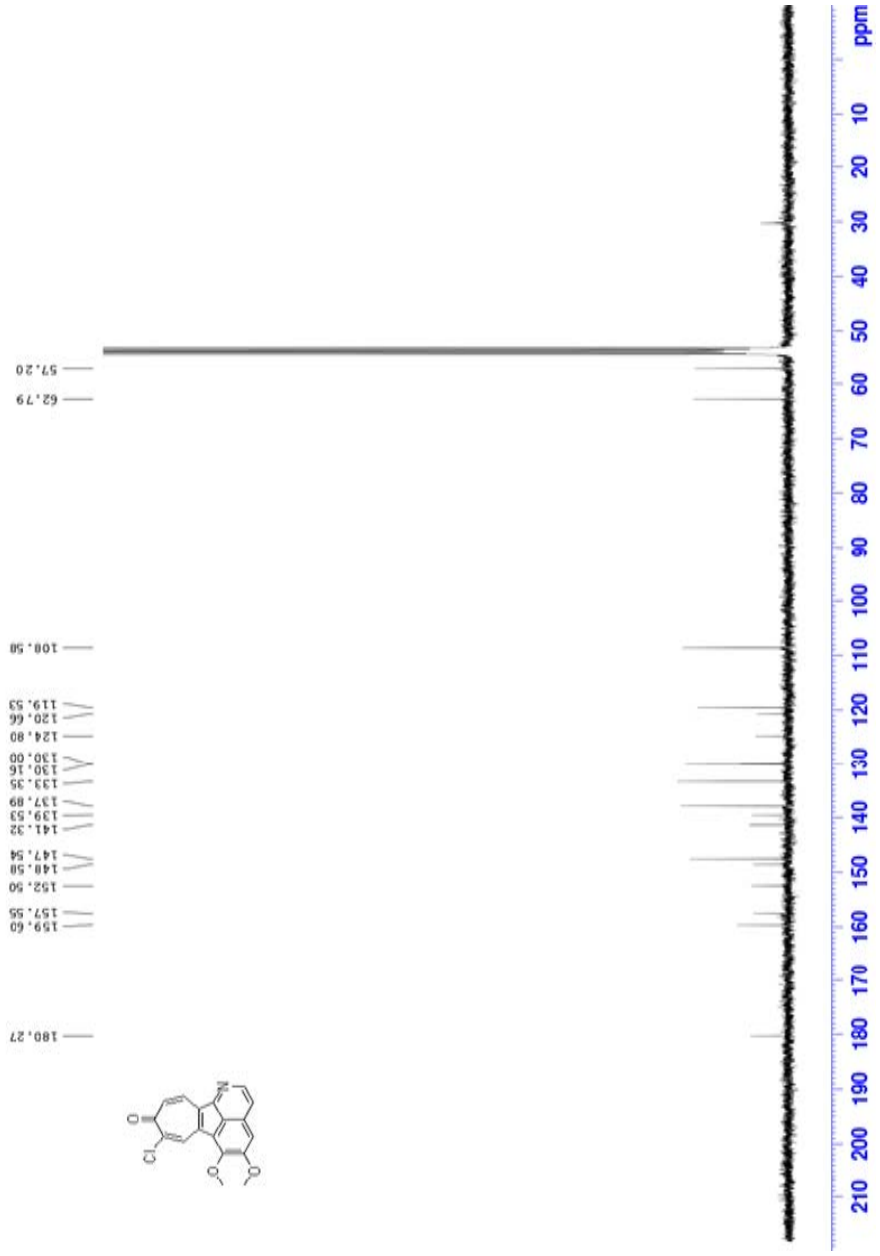
75 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1c**



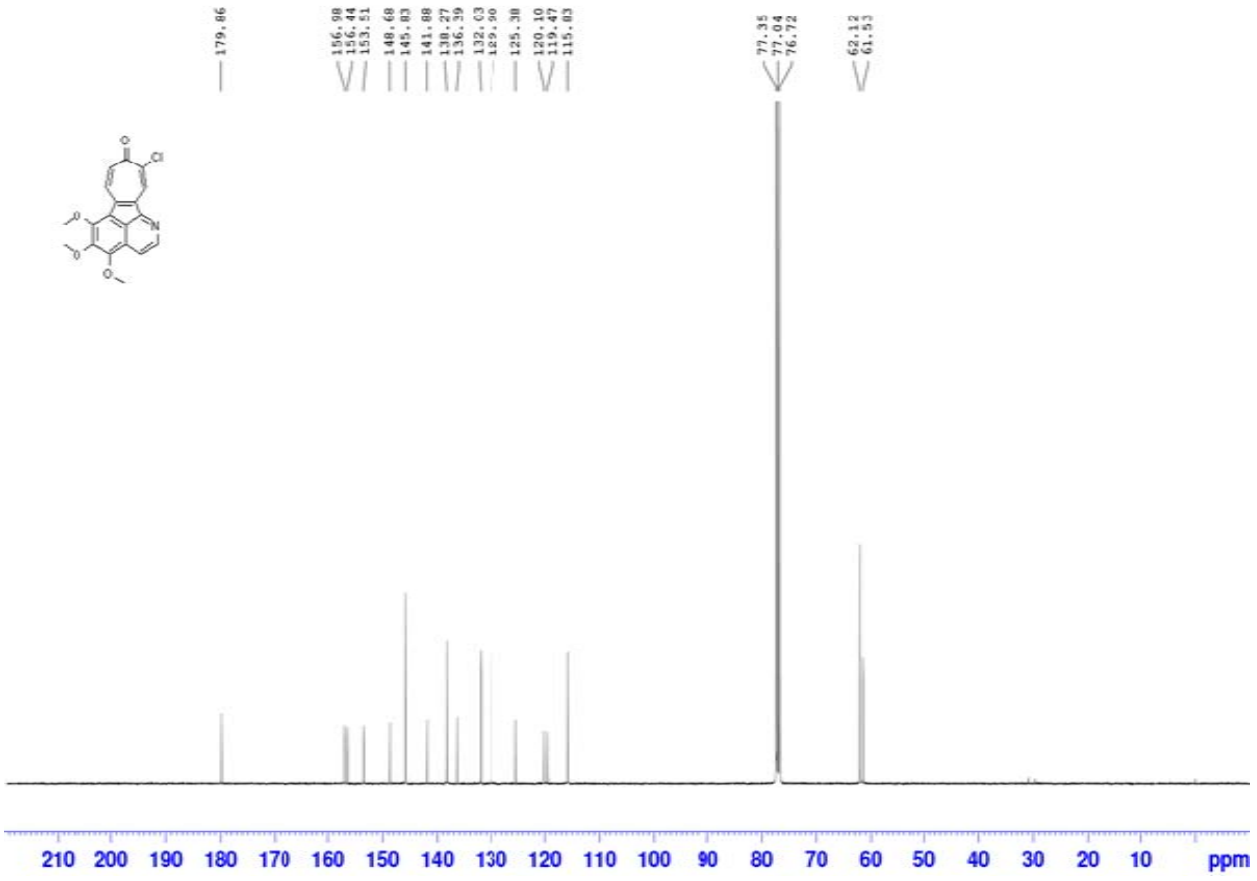
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1d**



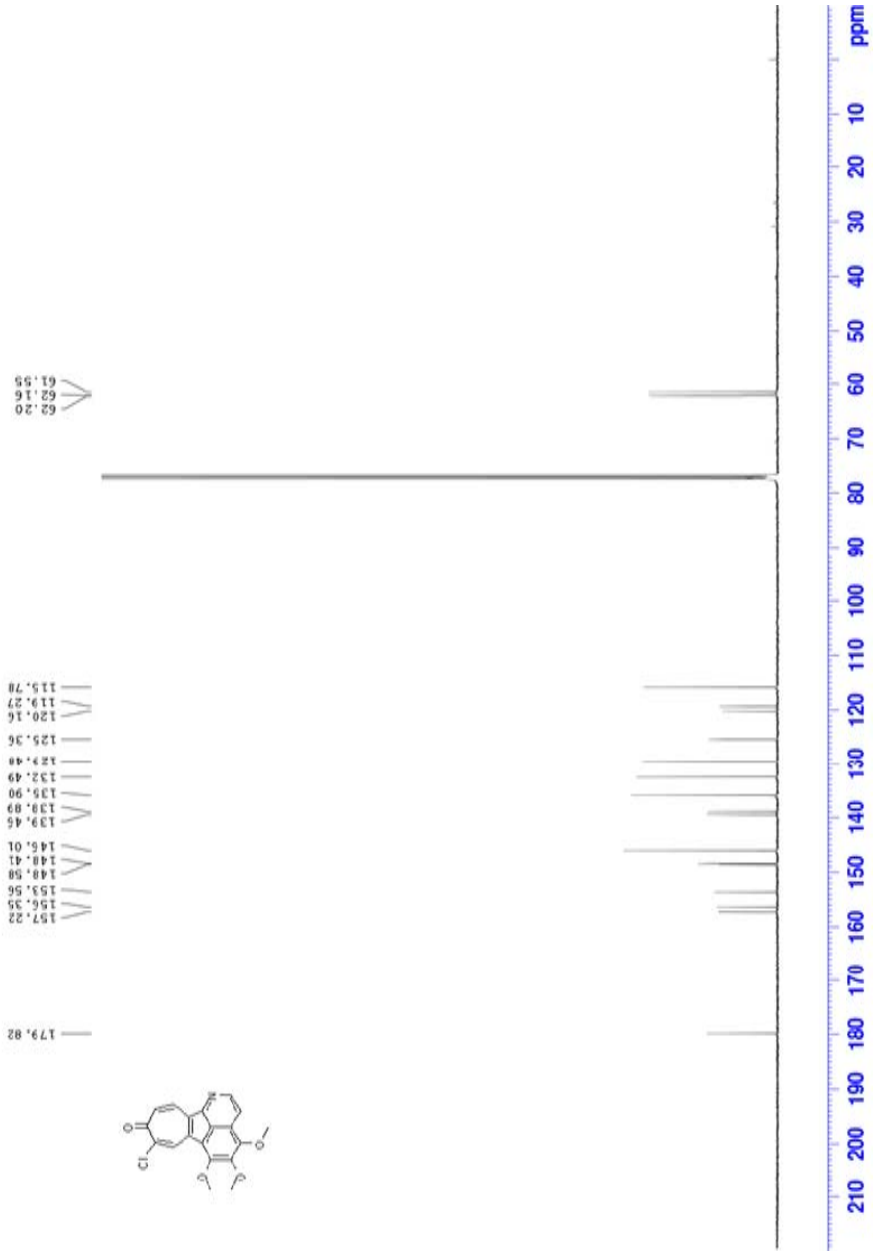
100 MHz ^{13}C-NMR spectrum (CD_2Cl_2) of compound **1ca**



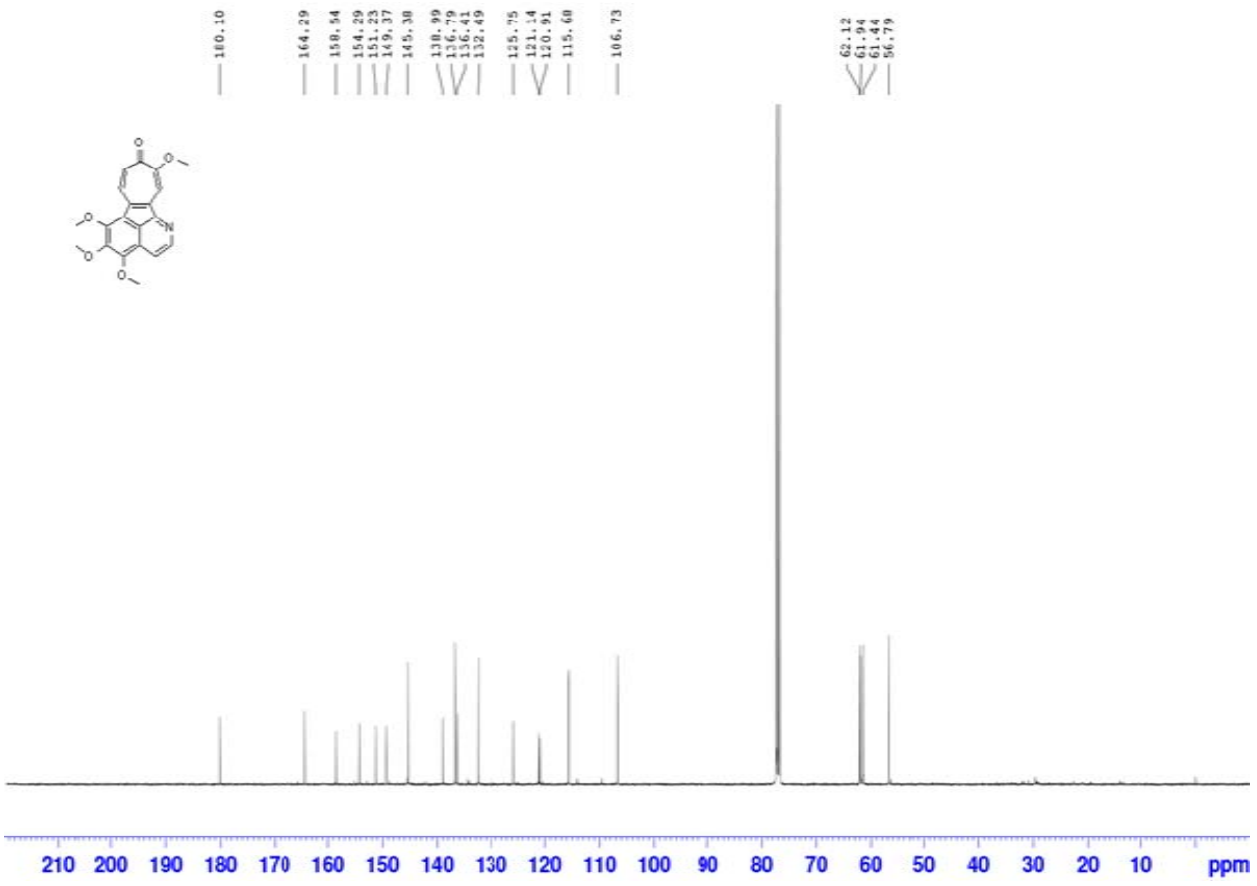
100 MHz ^{13}C-NMR spectrum (CD_2Cl_2) of compound **1cb**



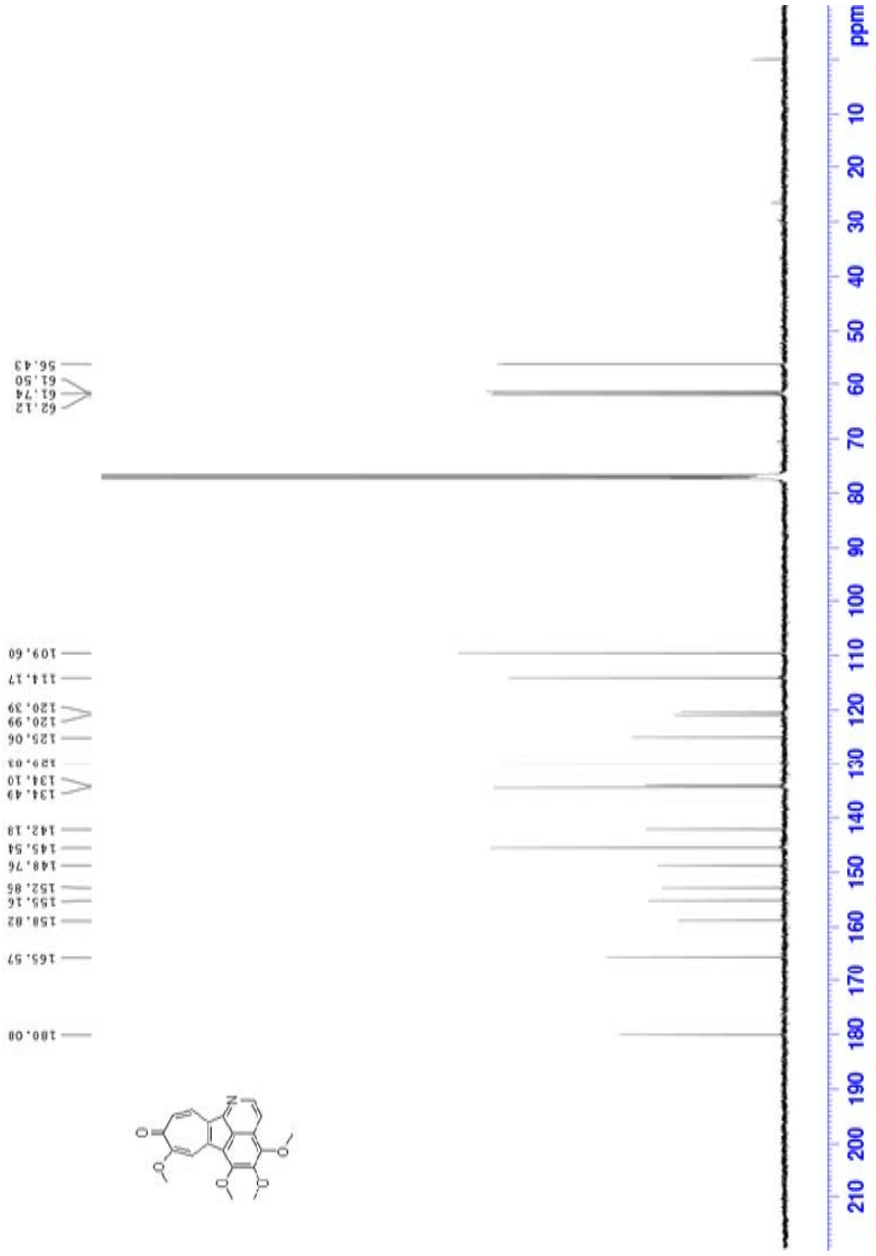
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1da**



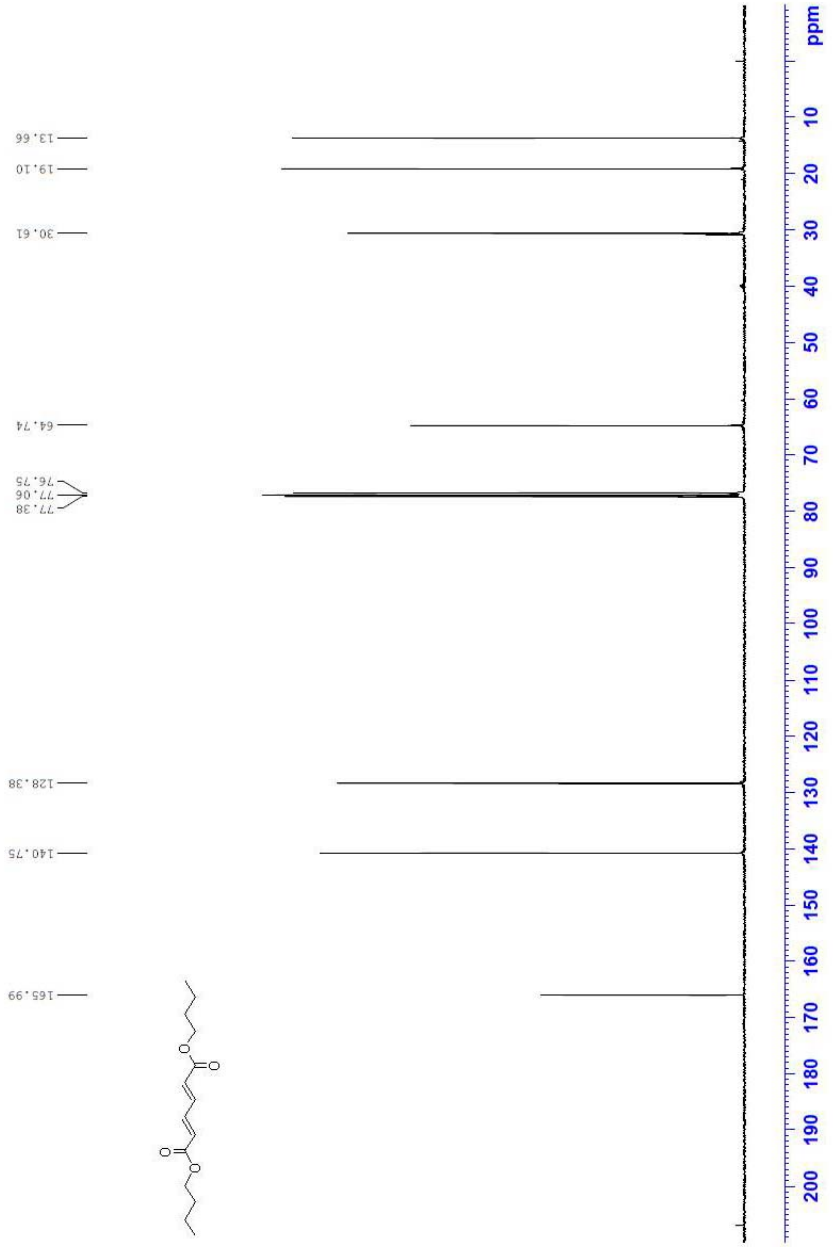
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1db**



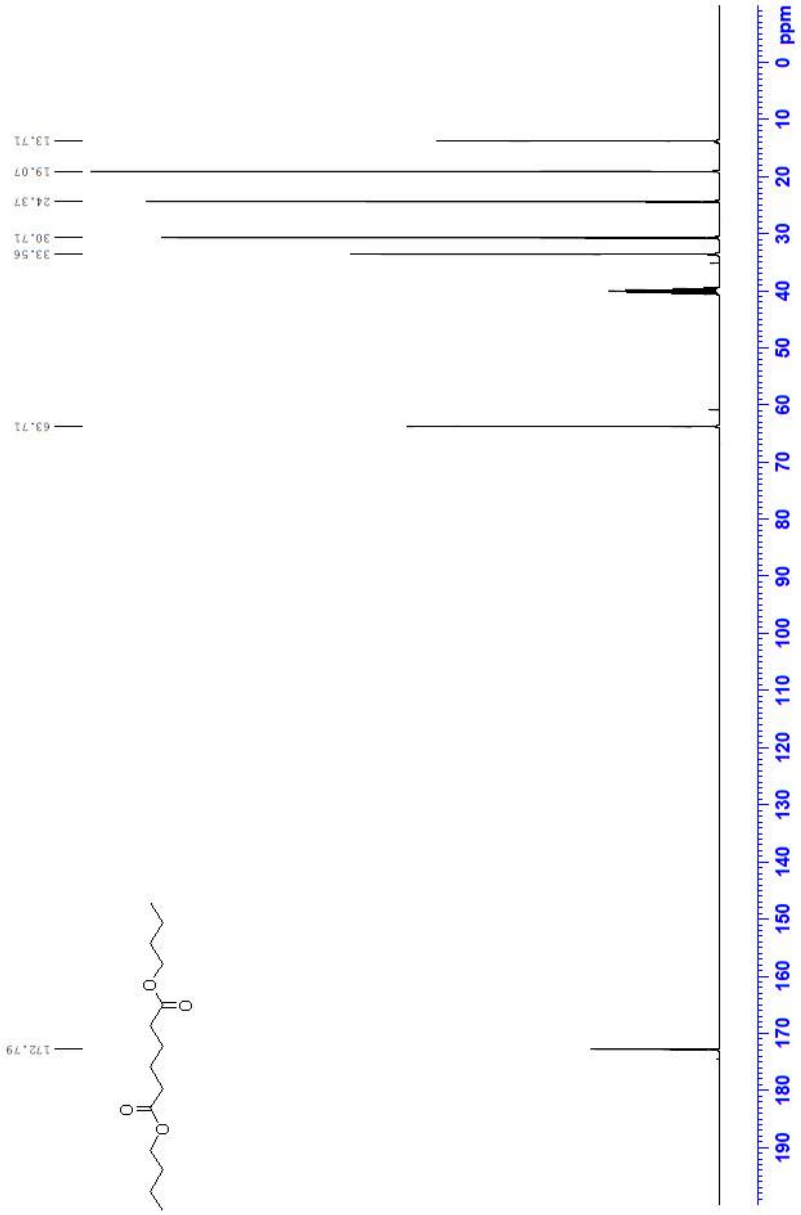
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1dc**



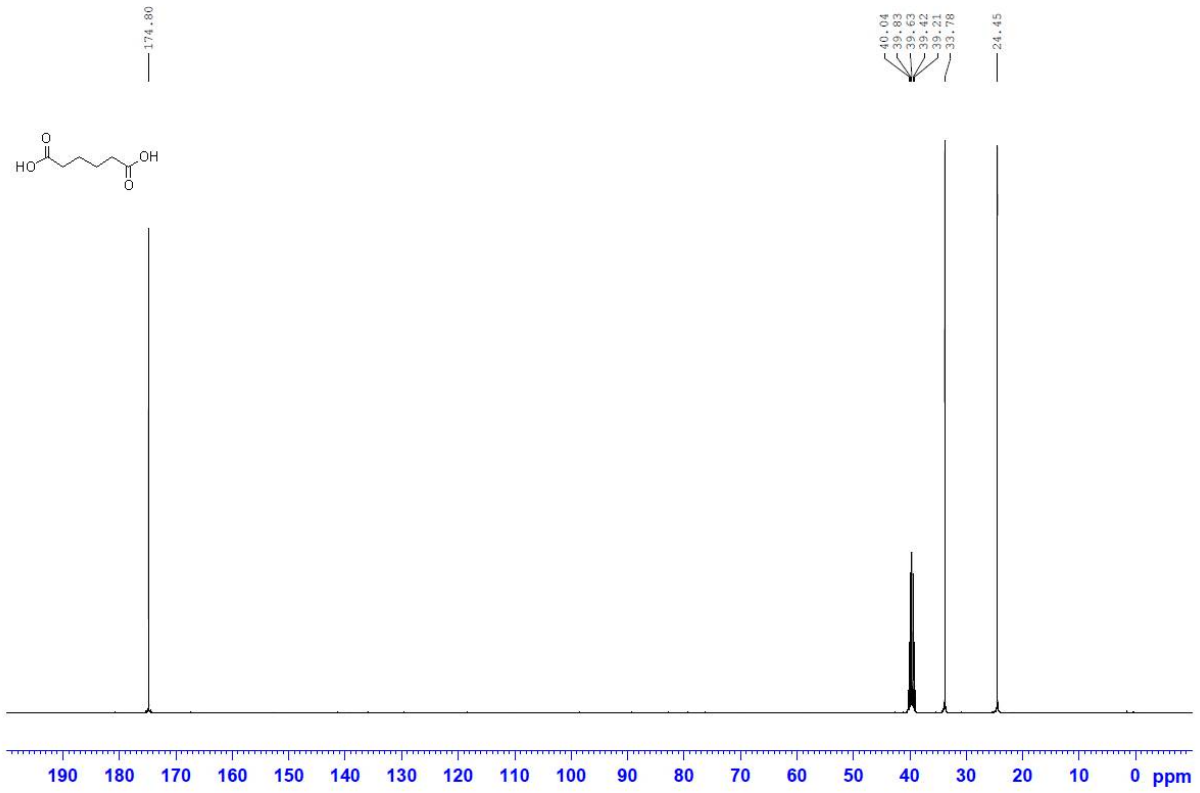
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **1dd**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **14a**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **15**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **16**

초 록

강력한 세포독성을 가진다고 알려진 트로폴로아이소퀴놀린의 보다 간결한 전합성 및 갈락토오스유래 아디픽산의 공정개발에 관한 연구가 수행되었다.

첫째로, 백혈병 세포인 P388에 대해 강력한 세포독성을 보이며 특징적인 아이소퀴놀린과 트로폰의 연결구조를 가지는 퍼레이트로폰 및 그 유도체들을 합성 하였다. 반응 기질별로 아이소퀴놀린 고리 구조 형성 효율이 상했던 직렬식 합성법의 단점을 보완하기 위해, 상업적적으로 구입이 가능한 브로모 아이소퀴놀린에 페놀을 도입해주는 병렬적인 합성 방식을 도입한 결과 총 5 단계를 거쳐 47%의 높은 수율로 퍼레이트로폰의 합성을 완료 하였다. 기질에 영향을 덜 받는 본 합성법의 장점을 이용하여 다양한 유도체가 효율적으로 합성되었으며, 그 중 염소가 도입된 유도체의 경우는 또 다른 트로폰 유도체의 합성을 위한 유용한 중간체로 쓰일 수 있다.

둘째로, 갈락토오스로부터 아디픽산을 합성하는 합성 공정에 대한 연구가 수행되었다. 지속적인 환경문제와, 원유의 고갈 문제를 가지고 있는 석유화학기반의 아디픽산 공정을 대체하기 위해, 동일한 탄소수를 가지는 갈락토오스 유래 갈락타릭산을 이용하여 바이오 기반의 아디픽산을 합성하였다. 본 연구에서는 실험실 규모의 반응에서 탈피하여 18 g 규모에서 64%의 수율로 바이오 기반 아디픽

산 합성에 성공하였다. 반응 규모가 커짐에 따라 심화되는 반응의 전환률 저하의 문제가 있었으나 에스터화 반응 및 단계적인 촉매 투입을 통해 개선하였고, 각 단계별로 수행되어야 하는 복잡한 정제 공정을 한 단계의 재결정만으로 단순화 하여 대규모의 원-포트 합성 공정을 수립하였다. 또한 이용되는 촉매의 비용 저감화를 위하여, 이온성 액체를 반응 매개로 최초로 도입하였고, 단, 5 mol%의 촉매만을 투입 후, 최대 10회까지 반복 사용 하여 특별한 수율의 저하 없이 매회 98% 이상의 높은 수율로 아디픽산의 중요 중간체인 뮤코네이트를 합성하였다.

주요어: 트로폴로아이소퀴놀린 알칼로이드, 음이온중합, 항백혈병효과, 바이오 기반 아디픽산, 탈산소탈수반응, 레늄, 이온성액체

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